The New England
Journal of Medicine

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Volume 255 DECEMBER 20, 1956 Number 25

HYPOPHYSECTOMY IN ADVANCED BREAST CANCER*

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THERE is undisputed evidence that the administration of steroid hormones or deprivation of hormone-producing tissues favorably modifies the anticipated behavior of advanced breast cancer. Extensive reviews have demonstrated the improvement that may be attained in selected patients after castration or adrenalectomy and the administration of estrogenic hormones, androgenic hormones or cortisone.[1,2] These methods of therapy have significantly altered the course of breast cancer to the extent that the lives of some patients have definitely been prolonged. It is postulated that the favorable responses occurring during hormonal therapy are mediated in part by suppression of the pituitary gland.[3] Recently, total surgical hypophysectomy has been employed in a further attempt to produce favorable regression of tumor masses in advanced breast cancer. The procedure has provided a means by which the mechanism of growth of breast cancer can be investigated further.

HORMONAL ASPECTS OF THE TREATMENT OF ADVANCED BREAST CANCER

The management of advanced breast cancer is dependent upon the age and menopausal status of the patient. It has long been recognized that in young women with osseous metastases an exacerbation of pain precedes the menstrual period and is associated with hypercalciuria and occasionally hypercalcemia due to rapid bone destruction. This has been objectively demonstrated by metabolic studies and establishes the fact that certain carcinomas of the breast are influenced by ovarian hormones.[1,4-6] Furthermore, the administration of estrogenic hormone in the presence of active ovarian function may sometimes accelerate the growth of breast cancer in the young woman. The demonstration that ovarian hormones influence the growth rate of breast cancer has provided a physiologic basis for treatment. A natural corollary is the fact that castration has become an accepted addition to the treatment of metastatic breast cancer in the premenopausal woman. Reports indicate that approximately 20 to 50 per cent of such patients obtain palliative benefit from castration. Paradoxically, an intensified growth of breast cancer in premenopausal women has been observed only rarely with administration of massive doses of estrogenic hormone (1000 mg. of stilbestrol a day). In fact, with these high levels, amenorrhea and regression of the tumor in a few patients has been noted.[1,5] It appears that these large doses of estrogen suppress the function of the pituitary gland so much that this effect is more important in inhibiting tumor growth than the stimulating effect of the estrogen administered.

Estrogenic hormones are therapeutically indicated primarily for advanced breast cancer in the postmenopausal woman. The administration of estrogenic hormones to elderly women has resulted in favorable objective remissions in 45 per cent of patients with soft-tissue manifestations of breast cancer and in 22 per cent of those with osseous metastases.[1] Androgenic-hormone therapy has been widely employed in the treatment of advanced breast cancer of all ages. These agents have appeared to be most efficacious in patients with osseous metastases. However, with the administration of androgenic hormones an induced hypercalcemia has been noted in 10 per cent of patients with osseous metastases.[7] This has been considered to be due to an acceleration of tumor growth and hence an increased rate of bone destruction. Recently, patterns of steroid excretion have been observed in patients with breast cancer receiving hormone therapy.[8,9] Estrone, estriol and estradiol have all been demonstrated to be excreted in a significantly increased amount during the administration of testosterone. It is now apparent that the androgenic hormone is converted in part to estrogen. This small amount of estrogenic product may be the factor that accounts for the stimulation and acceleration of tumor

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Supported in part by research grant C-2081 from the National Cancer Institute, National Institutes of Health, United States Public Health Service, by the American Cancer Society and by grant DRG-283 from the Damon Runyon Memorial Fund for Cancer Research.

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growth during the administration of androgenic hormone. To date androgenic hormones do not appear as effective objectively in suppressing tumor growth as castration in the premenopausal woman or estrogenic-hormone administration in the postmenopausal patient.

In premenopausal women castrated for advanced breast cancer the disease inevitably recurs. Enlargement of the adrenal glands in these patients has been noted, and was postulated to be the source of hormones causing the exacerbations of the cancer. Since the adrenal glands are a source of a multitude of hormones, including estrogens and androgens, it was apparent that removal of this gland might produce further control of the advanced breast cancer. Bilateral adrenalectomy has been demonstrated to induce significant objective remissions in patients with advanced breast cancer. There has been a close correlation between the response to castration and the subsequent response to adrenalectomy. The data indicate that failure to respond to castration means that there will be a failure to respond to adrenalectomy.[6] It appears appropriate to reserve total adrenalectomy for patients who have previously demonstrated a regressive response after castration.

Massive doses of cortisone have been employed in advanced breast cancer in an attempt to depress pituitary function and to produce secondary atrophy of the adrenal cortex. Objective regressions similar to those noted with other forms of hormone therapy have been observed. To date it appears that cortisone in doses of 300 mg. a day can be employed in patients previously castrated. Control of tumor growth and an unusual sense of well-being have continued for as long as a year in such patients.[10] The over-all effectiveness of this agent, however, has not been as complete as that with other methods of hormone therapy.

Rationale of Surgical Hypophysectomy

The pituitary gland has an increasingly apparent role in the control of growth of breast cancer. It is well established that gonadotrophic hormone directly controls ovarian function and the production of estrogenic hormone. Similarly, ACTH hormone provides a stimulus to the adrenal cortex to increase its production of steroid hormones. In patients undergoing castration for advanced breast cancer, the pituitary and adrenal glands later increase in size. This hypertrophy may represent the source of hormonal agents important in the subsequent exacerbation of the disease. The pituitary gland appears to be a source of specific hormonal factors involved in the acceleration or maintenance of tumor growth in breast cancer. Animal experiments demonstrated that hypophysectomy in rats definitely retarded the growth of tumors beginning from the day of extirpation of the hypophysis.[11] Hypophysectomy caused 11.5 per cent of spontaneous mammary tumors in mice to regress.[12] Growth hormone has been administered to animals in an attempt to evaluate its effect on normal and abnormal growth. Neoplasms of organs other than the pituitary gland occurred much more frequently in rats injected with growth hormone than in the controls.[13-15]

It has been demonstrated that growth hormone has a direct effect on promotion of tumor growth in the human patient. The administration of growth hormone to patients with advanced breast cancer has caused an increased growth rate of the pathologic process. When it was administered to 2 patients after hypophysectomy, an increased urinary calcium excretion occurred.[16-19] Furthermore, aggravation of advanced prostate cancer has also been noticed during growth-hormone administration.[20,21]

It has been postulated that the ameliorative effects of the administration of sex hormones in patients with advanced cancer of the breast may be due to the fact that in massive doses these hormones depress pituitary function and produce a "chemical hypophysectomy."[3] To substantiate this the incidence of peripheral cancer in Simmonds's disease has been recorded. Cancer of the breast or ovaries has not been observed in association with Simmonds's disease, whereas cancer of the cervix, thyroid gland and other organs has been noted.[22]

Attempts to produce pituitary suppression by irradiation of the pituitary gland have failed. The administration of as much as 10,000-r tissue dose to the pituitary gland in women with metastatic breast cancer resulted in no clinical or laboratory evidence of hypopituitary function, nor was the growth of the neoplasm affected.[23] It was inevitable that total surgical hypophysectomy would be employed in an attempt to control metastatic breast cancer.

Hypophysectomy in Various Diseases

Total hypophysectomy has long been considered in the treatment of various diseases. The procedure has been carried out in Cushing's disease,[24-27] epilepsy,[28-31] diabetes mellitus,[20,26,27,32-37] malignant hypertension,[26,27] adrenal carcinoma,[32,38,39] prostatic carcinoma,[17,26,27,32,40,41] hypernephroma,[17,26,27] chorioepithelioma,[17,26,27,40] malignant melanoma,[17,38,40,42] thyroid carcinoma,[17,40] ovarian carcinoma,[17,32] reticulum-cell sarcoma,[17,40] malignant exophthalmos,[43] breast cancer in women[17,18,20,26,27,32-34,40,44-51] and in men,[40,46] pancreatic cancer[40] and testicular cancer.[18]

Improvements have been reported in Cushing's disease, diabetes mellitus, hypertension, prostatic carcinoma, chorioepithelioma, malignant exophthalmos and breast cancer.

Hypophysectomy in Breast Cancer

Since 1951 the availability of ACTH and cortisone has allowed an intensive investigation of the effects

of hypophysectomy in patients with neoplastic disease. Of 50 patients with metastatic breast cancer described by Luft and Olivecrona[34,46] 20 demonstrated subjective or objective improvement for periods lasting three to twenty-seven months. Pearson et al.[18] reported objective remissions in 21 of 41 patients who could be evaluated of a total of 58 patients operated on. Subsequently, in an extension of the same series, Ray[40] reported on the results in 67 patients surviving in a group of 74 patients. Objective regressions occurred in 28 patients, 8 others demonstrating apparent arrest of the process. Similar types of regressions have been reported by other investigators.[32,33,38,40,44,45,47,50] The present report is our experience to date.

Material

Thirty-four patients were selected for total hypophysectomy. In 2 of these the operative procedure was discontinued when profuse bleeding was encountered from extensive metastatic carcinoma of the skull and meninges at the site of the bone flap. Four patients recently operated on are not included in this report. The results, therefore, are based upon 28 patients in whom a total surgical hypophysectomy was performed more than three months before analysis. Though relief of pain and increased well-being occurred, only objective responses are regarded as a favorable result of the hypophysectomy procedure. Metabolic observations were conducted in selected patients to establish a measure of the rate of tumor growth or tumor regression and the function of the pituitary, thyroid and adrenal glands and ovaries. Though there is no established test that records the complete removal of the pituitary gland, a measure of the function of the end organs has been employed to evaluate crudely the degree of decreased control by the pituitary gland.

Preoperative Management

In addition to the usual preoperative evaluations of the endocrine glands and status of the tumor, a recording of the status of the eyes and visual fields was conducted. An x-ray film of the skull was obtained to establish the presence of skull metastases. Bleeding and clotting times and a platelet count were shown to be normal, and serum electrolytes and blood urea nitrogen were determined before any steroid therapy was administered.

Cortisone was begun not less than two days preoperatively in a dose of 100 mg. every twelve hours intramuscularly. Because of the possible replacement of the adrenal glands by tumor, ACTH was not employed. On the morning of the operation an extra 100 mg. of cortisone was given orally. Endotracheal anesthesia with Pentothal, curare and nitrous oxide was employed routinely. No anesthetic complications arose.

Operative Technic

The incision is the usual incision made for transfrontal craniotomy, located above the hairline to obtain concealment. The scalp flap is turned forward and lateral. A bone flap is then reflected laterally, pedicled on the temporal muscle. This bone flap extends to the mid-line and forward to just above the frontal sinus. In 33 cases the operation was done on the right. In 1 case the operation was performed on the left because of the presence of extensive metastases on the right side. The exposed dura is opened by reflection of a flap medially. This dural flap is 3.5 to 4.0 cm. wide and extends from the anterior edge of the bone flap back almost to the coronal suture. A block of the anterior medial portion of the frontal lobe is then removed extending directly down through the lobe from the edges of the sectioned dura and extending forward to the frontal pole. The posterior edge of the excision comes directly down on the optic chiasm with the anterior communicating arteries overlying it. This wide exposure of the pituitary fossa is attained without any retraction of the remaining portion of the frontal lobe. Resection of the frontal lobe has eliminated the complication of postoperative cerebral edema and increased intracranial pressure, which might occur if the frontal lobe were forcibly retracted. When the chiasm is prefixed, the tuberculum sellae and the medial part of the medial clinoid processes are removed to obtain better exposure of the anterior part of the sella turcica. This is accomplished by perforation of the tuberculum sellae with a small chisel and then rongeuring away of the bone. With a narrow retractor the optic chiasm is gently lifted to expose the pituitary stalk passing backward and upward behind the chiasm. The stalk is picked up with a hook and held forward while a silver clip is put on it above the hook, and then the stalk is cut. The diaphragma sellae has an opening of variable size through which the stalk passes. This opening is enlarged by blunt dissection by insertion of the tip of a pointed hemostat and spreading the edges apart. The upper surface of the pituitary gland is thus widely exposed, and an attempt is then made to separate it around its periphery and shell it out of the fossa. Sometimes, it is possible to shell out most of the pituitary gland in one smooth-walled piece, but invariably some fragments remain attached to the wall of the fossa. These are then curetted out. Most of the wall is then easily inspected and seen to be free of gross remnants of pituitary gland. The undersurface of the margins of the diaphragma sellae cannot be seen, and one must depend upon the curette to get all fragments from this site.

There has been no difficulty with hemorrhage during removal of the gland in any case of hypophysectomy for breast carcinoma. Hemorrhage has been so moderate or easily controlled that good visualization has been possible throughout the procedure of the removal of the gland and a dry cavity can be well

inspected after removal. Estimated blood loss as a rule has not exceeded 500 ml.

The variable position of the optic chiasm in relation to the pituitary gland depends upon the length of the intracranial segment of the optic nerves. In 22 patients this segment was long, so that most or all of the pituitary gland was anterior to the chiasm; in 3 the chiasm was forward over the gland so that only a small portion of the gland presented anterior to the chiasm, and in 3 the chiasm was far anterior so that no pituitary gland presented anterior to it and only a few millimeters of space existed between the tuberculum sellae and the chiasm. In these cases the tuberculum sellae was removed for better exposure of the pituitary fossa.

Postoperative Management

Postoperatively, parenteral fluid administration was limited to no more than 2500 ml. daily in an attempt to avoid overloading with water and possibly contributing to cerebral edema. Prophylactic antibiotic therapy consisted of streptomycin, and penicillin was employed in all cases. Cortisone, 100 mg. every twelve hours intramuscularly, was administered until the patient could take cortisone by mouth. The dose was then gradually reduced to a daily maintenance level of 50 mg. orally. Most patients were able to take fluids by mouth on the first postoperative day and began eating on the second or third day. One week after operation administration of 120 mg. of thyroid was begun in patients in whom no subsequent thyroid studies were being conducted, but in some cases thyroid was not given until investigative data had clearly illustrated hypothyroidism. No Pitressin was administered until the end of at least the second week, so that it could be established whether or not the polyuria and polydipsia that occurred were temporary or permanent.

Results

Twenty-eight patients have undergone total hypophysectomy for advanced carcinoma of the breast (Table 1). At least three months have elapsed since the last operation — sufficient time to allow evaluation of whether or not the tumor will regress.

Eighteen of the 28 patients have had objective regressions. These are similar to those noted with other forms of hormone therapy. Improvement was manifested by recalcification of osteolytic metastases, decrease in size of pulmonary lesions or disappearance of pleural effusion, disappearance of cutaneous lesions and lymph nodes, decrease in the size of the liver and reduction of an elevated serum alkaline phosphatase due to liver metastases. Recalcification of osteolytic lesions was noted in 12 patients, and reduction in size or disappearance of pulmonary or pleural metastases in 5, of cutaneous lesions in 5, of lymph nodes in 2, of liver metastases in 2 and of a metastatic lesion compressing the spinal cord in 2. In the other 10 patients there was no evidence of objective improvement, but 2 of them had evidence of improvement during a metabolic study, with decrease in hypercalcemia and hypercalciuria, increase in serum alkaline phosphatase consistent with bone regeneration and relief of pain. One of these 2 patients died of meningitis twenty-two days after operation. It appears that the growth rate of the breast cancer had been favorably altered in both cases.

Subjective improvement was noted in 20 patients. This consisted of an increased feeling of well-being or relief of pain. In 4 patients in whom striking relief of pain occurred, there was no objective evidence of regression. In 1 patient who was asymptomatic there was no change in subjective feelings. In 7 patients there was absolutely no evidence of either objective or subjective improvement after the hypophysectomy. Two of these, however, survived for less than four days and cannot be truly evaluated in terms of a tumor regression.

The longest duration of an objective response has been twenty months. In this case reactivation has occurred. Reactivation also occurred in patients demonstrating objective responses after three, three, five, six, six, eight, nine, eleven, eighteen and twenty months. At present 7 patients are still maintaining the initial objective improvement at three, five, four, five, eight, ten (2 patients) and thirteen months. One other patient, who died within the first month, had demonstrated definite objective improvement. The longest survival has been thirty months.

Table 1. *Data on Average Survival and Regression.*

Datum	No. of Patients	Months
Average survival:		
Entire series	28	7.8+
Survival for >2 mo. after operation	23	9.3+
No response	10	2.8
Response followed by reactivation	11	12.4+
Still in remission	7	7.6+
Average survival of dead patients:		
All	15	6.8
Living for >2 mo. after operation	10	9.9
Average survival of living patients:	13	9.0+
Reactivated disease	5	12.0+
Still in remission	7	7.7+
No response	1	3.0+
Average duration of regression:	18	8.1+
Reactivation	11	8.5
Still in remission	7	7.6+

Of the 28 patients treated 15, 6 of whom had demonstrated objective regression, are now dead. One of these lived for thirty months. Thirteen patients are now alive three and a half to twenty months after hypophysectomy, and 12 have demonstrated objective

regressions. Calculation of the survival times supports the concept that in individual cases life has definitely been prolonged as a result of the operative procedure.

The average survival of the entire series was more than seven and eight-tenths months. The nonresponding group survived for two and eight-tenths months. Patients demonstrating a regression after hypophysectomy, followed by reactivation of the disease, have survived for an average of twelve and four-tenths months or more to date. Those still in remission have survived for an average of seven and six-tenths months or more.

The 13 living patients have survived for an average of nine months or more. Five in whom reactivation of the disease has occurred have survived in excess of twelve months, and those still in remission have survived for more than seven and seven-tenths months.

The average duration of regression in 18 patients has been eight and a tenth months or more. In those with reactivation the regressions average eight and a half months; those still in remission have averaged in excess of seven and six-tenths months, and this figure will increase as the regressions are maintained.

Further evidence of tumor improvement has been demonstrated by metabolic investigations conducted in 9 selected patients. In those demonstrating objective regressions the metabolic alterations consisted of a decrease in serum calcium in patients with hypercalcemia, decrease of urinary calcium excretion, increase in serum alkaline phosphatase, positive nitrogen balance postoperatively and weight gain.

One metabolic investigation demonstrated the rapid effect that hypophysectomy may have on advanced breast cancer (Fig. 1). A thirty-eight-year-old woman had extensive osteolytic metastases, nausea and vomiting. Metabolic investigations demonstrated a serum calcium of 16 mg., serum phosphorus of 4 mg. and alkaline phosphatase of 3.1 Bodansky units per 100 ml. On a dietary intake of 180 mg. of calcium per day the urinary calcium measured 440 to 500 mg. a day. Immediately after the hypophysectomy there was a decrease in serum calcium and urinary calcium and an increase in serum alkaline phosphatase. On the fourteenth postoperative day the serum calcium was 9.4 mg., the serum phosphorus 2.9 mg., and the serum alkaline phosphatase 5.4 Bodansky units per 100 ml. On the same dietary intake of calcium the urinary calcium was 10 mg. a day. Subsequently, the patient demonstrated a striking remission, with relief of pain and recalcification of the bones.

Complications

It is not unexpected that, with major surgery of this sort, complications arise. During this course of our experience 3 patients were selected for operation who would now be regarded as poor operative risks. In 5 patients temporary rhinorrhea occurred immediately after the operation. This was a result of puncturing the sphenoid sinus in the process of removing the tuberculum sellae. In 1 of these patients meningitis occurred. Postoperative headaches appeared in almost all patients, but the intensity varied. There was no difficulty in controlling this pain, which persisted for only a few days.

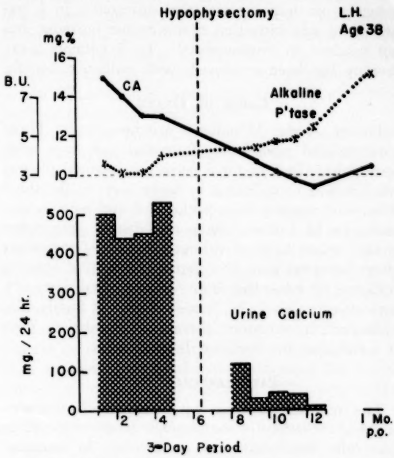

FIGURE 1. *Metabolic Response after Hypophysectomy in Case 22, a Thirty-eight-Year-Old Woman.*

The patient was on a constant diet including 180 mg. of calcium and neutral ash. Hypercalcemia and hypercalciuria decreased to normal levels.

In 3 cases postoperative meningitis developed. One patient, who preoperatively had a severe hypercalcemia and uremia with confusion, continued to be confused after operation though the serum calcium and urinary calcium decreased to normal levels. No localizing signs occurred, and the patient died of a meningitis twenty-two days postoperatively. At autopsy there was an *Escherichia coli* meningitis with a localized abscess at the base of the brain. In 1 patient with rhinorrhea a proteus meningitis occurred. After chloramphenicol therapy, there was a complete remission of the meningitis; this patient was the longest-surviving patient in this series. A third patient had a paracolon meningitis six days postoperatively but recovered after chloramphenicol, tetracycline and sulfadiazine therapy.

A permanent visual disturbance occurred in 2 patients postoperatively. In 1 there was an immediate postoperative loss of peripheral vision of the right eye; the second patient had loss of vision in the right eye six days postoperatively, concomitant with the development of a paracolon meningitis. In only 1 patient has there been loss of smell.

Subsequent Tumor Therapy

In patients in whom a regression followed hypophysectomy consideration was given to the possible means of treating the disease when reactivation occurred. Eight patients received other forms of therapy after evidence of reactivation of the disease appeared. Androgenic hormones in this group produced objective regressions in 3 patients. In 3 others, however, no response was demonstrated. In 2 patients the administration of estrogenic hormone has not resulted in improvement. In 2 patients x-ray therapy has been employed, with palliative benefit.

Cause of Death

Fifteen of the 28 patients are now dead. Three patients died twenty-five, four and two days postoperatively. In 2 of these persistent bilateral pleural effusion was complicated by atelectasis; in the third there were massive liver, pericardial and bone metastases. In 10 patients death was due to progression of the cancer, with or without evidence of regression after the operation. One patient, who had striking evidence of subjective improvement, died forty-one days postoperatively at home when her family discontinued the cortisone therapy. One patient died of meningitis and localized brain abscess.

Pathological Data

The removal of fresh pituitary glands provides material for extensive morphologic study of the pituitary cells. Such studies are under way. In examination of the removed brain tissue multiple small areas of cancer cells have been noted. The extensive nature of metastatic cancer was realized in 1 patient, in whom clusters of cancer cells were present in the pituitary gland. In another a dural meningioma was removed at operation.

In 5 patients autopsy examination has included removal of the sella turcica. In 1 patient there has been microscopical evidence of pituitary cells. In the other 4 patients there was no evidence of viable pituitary tissue, though serial sections of the entire fossa were not obtained.

Endocrinologic Aspects of Hypophysectomy

The chief problem in hypophysectomy is the subsequent evaluation of the degree of completeness of removal of the gland. There is no adequate test of pituitary function sufficiently sensitive to establish this fact. Only post-mortem examination of the fossa by serial sections can determine the presence or absence of cells. A measure of the endocrine glands dependent upon pituitary function provides a crude test of the degree of pituitary removal.

Adrenal Glands

The patient with advanced breast cancer is frequently debilitated, as manifested by adrenal-function tests. The urinary 17-ketosteroids in most of the patients were low. After the hypophysectomy a decrease to 1 to 3 mg. per twenty-four hours occurred. Eosinophil tests of adrenal function were of no value. In all cases in which attempts were made to withdraw cortisone, a drop in blood pressure, fever and collapse resulted, indicative of adrenal insufficiency. One patient died at home four days after the family stopped cortisone therapy. Further evidence of diminished adrenal function was the decrease in growth of axillary hair that followed hypophysectomy.

Ovaries

Many of the patients had been castrated or had undergone a spontaneous menopause. In 2 patients with normal menstrual periods amenorrhea followed the hypophysectomy. Measurement of pituitary gonadotrophic hormone revealed a disappearance of this hormone after hypophysectomy, and in no case has it subsequently reappeared in the urine.

It has been suggested that improvement in the menopausal syndrome treated with hormones results from inhibition of follicle-stimulating hormone. Hot flushes followed hypophysectomy in 1 patient, who menstruated regularly before the operation. In 3 patients with hot flushes after castration, there was no change in the intensity of flushes before the hypophysectomy. Contrary to present belief, it appears that inhibition or removal of follicle-stimulating hormone is not directly responsible for the control of the symptoms of the menopausal syndrome.

Thyroid Function

After hypophysectomy the thyroid function of selected patients was studied. The onset of clinical hypothyroidism was varied. Usually within three months of the hypophysectomy patients noted dry skin, decreased sweating, cold intolerance, constipation, weight gain and poor regrowth of scalp hair. Subsequently, sluggish behavior, myxedematous facies and slow return of tendon reflexes were noted.

Thyroid-function tests demonstrated a decrease to hypothyroid levels. In all cases the uptake of radioactive iodine, basal metabolism rate and serum protein-bound iodine became low. The serum cholesterol had not consistently increased to hypothyroid levels within the four-month postoperative period. Similar observations of thyroid function after hypophysectomy have been noted by other investigators.[52]

Diabetes Insipidus

The development of polydipsia and polyuria after hypophysectomy has provided a unique opportunity to investigate the physiologic mechanisms of diabetes insipidus. In all but 1 patient some degree of abnormal water balance was noted postoperatively. Within twenty-four hours of the operation 26 patients demonstrated polyuria and polydipsia. The subsequent pattern of water excretion can be divided into three groups: immediate and permanent polyuria; immediate polyuria for one to six days, followed by a period of normal urinary volumes up to four

weeks and subsequent permanent polyuria; and delayed development of temporary polyuria thirty-five and sixty days after operation in 2 patients. One patient with Type A and 1 with Type B had persistent polyuria for only five and six months.

The volume of urine varied considerably. The maximum daily excretion was 16,000 ml. Though the specific gravity was usually less than 1.005, concentrations up to 1.020 were noted in several patients with clinical diabetes insipidus. The responses to hypertonic saline tests were abnormal. Antidiuretic therapy was not instituted in any case until the pattern of water excretion was established. Because of the difficulty encountered in maintaining constant control with Pitressin tannate, Pitressin powder by nasal insufflation has been employed. Pitressin was not administered unless the patient complained of the volume of water ingested or had disturbing nocturia. Pitressin was given to 14 patients, 1 of whom discontinued the hormone after six months. Thirteen patients have been permanently maintained on Pitressin, requiring one to six jets per nostril per day.

The initial transient polyuria may be assumed to have been due to operative damage to the remaining cells in the hypothalamus and hypophyseal stalk producing antidiuretic hormone. Only a few viable supraoptic cells need remain to prevent polyuria.[53] It was earlier suggested that diabetes insipidus was more common when the hypophysectomy was incomplete.[54] There was no correlation with the development of diabetes insipidus and the response of the cancer. Nor was there any correlation, as far as we can determine from our data, between the completeness of hypophysectomy and permanent polyuria.

Discussion

Alteration of the hormonal status of the patient with advanced breast cancer may profoundly influence the course of the disease. Such alterations also may occur spontaneously and may account for the wide variations in the course of untreated breast cancer. The destruction of the ovaries, adrenal glands and pituitary gland has been demonstrated with breast cancer and may explain some of the alterations in the tumor. Modes of action of hormonal therapy are subtle. Even though the precise mechanisms cannot be defined, observations have suggested that tumor growth is governed by the current endocrinologic status of the host. It appears that in breast cancer the maintenance and growth of the tumor is dependent upon hormonal factors of the ovaries, adrenal glands and pituitary gland. No one of these factors alone is the major one. Yet the relative imbalance of the hormonal status attained by administration or deprivation of hormones may be truly as important as the total withdrawal or administration of specific agents.

Invariably, breast cancers that regress after hormonal alteration will eventually undergo reactivation. The more resistant tumor cells may adapt themselves to the environment initially rendered unfavorable to tumor growth.[2] Repeatedly favorable responses may occur when the initial therapy is abandoned or when other hormonal therapy is instituted. Hypophysectomy provides another means of altering the metabolic status of the patient.

Total hypophysectomy has been attempted in patients with advanced breast cancer because of the observation that estrogenic hormones, androgenic hormones and growth hormone are, under certain physiologic conditions, a stimulus to the growth of breast cancer. The removal of the pituitary gland would eliminate the stimulating factors and induce another hormonal imbalance.

Twenty-eight patients with advanced breast cancer have undergone total hypophysectomy. Eighteen of these have demonstrated striking objective clinical regressions. The longest sustained remission was twenty months. Two additional patients gave metabolic evidence of decreased rate of tumor growth. Of the 28 patients 7 are still being observed during a remission from three and a half to thirteen months after hypophysectomy. Thirteen patients are alive at the time of this report. Furthermore, the average survival of patients demonstrating tumor regressions has far exceeded that of those without improvement. It is apparent that total hypophysectomy has a definite role in the management of advanced breast cancer.

The severity of the operation necessitates careful selection of the patient for hypophysectomy. All patients of this series who had undergone castration for metastatic breast cancer and had demonstrated a response to castration subsequently, when the disease progressed, had a regression after hypophysectomy. In other words, in the treatment of advanced breast cancer, a patient responding to castration will subsequently respond to hypophysectomy. The knowledge that a metastatic disease has responded to castration appears to support the premise that prophylactic castration at the time of radical mastectomy should not be carried out, but should be reserved for control of the metastatic disease once it is manifest. In the postmenopausal woman, in whom estrogenic hormone is most commonly employed, it also appears that, upon reactivation of the disease during estrogen therapy, hypophysectomy will result in a further remission.

Hypophysectomy eliminates the pituitary hormones as well as profoundly suppressing ovarian and adrenal function in a way comparable to the removal of these endocrine glands. In view of the favorable responses after hypophysectomy, the concomitant adrenal atrophy and the ease in managing the patient, it appears that hypophysectomy is to be preferred over adrenalectomy in the treatment of advanced breast cancer. There is insufficient evidence, as yet, that hypophysectomy should be employed as the initial endocrine treatment for patients with

metastatic breast cancer. However, if hypophysectomy could have an effect equal to the sum of oöphorectomy, adrenalectomy and hypophysectomy, hypophysectomy might become the preferred initial endocrine treatment for metastatic breast cancer in selected cases. Investigations of this sort are being explored at present.

Eventually, breast cancers regressing after hypophysectomy undergo reactivation. The role of functioning accessory pituitary tissue in the exacerbations cannot be determined yet. Accessory anterior-lobe tissue has been described in the pharyngeal mucosa and sphenoid bone and with the sella turcica.[55,56] A pharyngeal pituitary gland has been described in over 90 per cent of autopsies.[57] In cases of destroyed activity of the pituitary gland it is theoretically possible that the pharyngeal pituitary gland undergoes alterations and serves as an endocrine organ.

Summary and Conclusions

Total surgical hypophysectomy is of specific value in the management of advanced breast cancer in selected cases. Objective improvement occurred in 18 of 28 patients treated. Metabolic remissions were observed in 2 additional patients.

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A COMPARISON BETWEEN PROTOVERATRINE A AND PROTOVERATRINE B ORALLY IN ARTERIAL HYPERTENSION*

A Therapeutically Important Difference in Activity

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DERIVATIVES of veratrum plants have been shown to be useful agents in the management of hypertension[1-6] and eclampsia.[7-9] Mixtures of veratrum alkaloids have potent hypotensive and bradycrotic activity. The limiting factor in the clinical use of these drugs has been the narrow dosage range between hypotensive and emetic effects. By the intravenous route there has been a high degree of reproducibility of nonemetic hypotensive responses in individual patients. However, orally, considerable variability in response has been common, making the long-term use of these drugs difficult in some patients.

Evidence that different veratrum alkaloids have differing pharmacologic effects[10] has encouraged the study of pure veratrum alkaloids. When "protoveratrine" was introduced into clinical medicine, it was considered to be a single alkaloid. It has since been shown to be a mixture of two alkaloids, protoveratrine A and protoveratrine B, each of which is a tetraester of the alkamine, protoverine[11] (Fig. 1). These alkaloids differ chemically by one hydroxyl group.

Although it has been believed that the pharmacologic differences between these two substances were small[12] and of little clinical significance[13] I have observed marked differences in activity when these agents are administered orally in hypertensive patients. Since the observations have therapeutic significance, the cases are reported in detail.

MATERIAL AND METHODS

The hypotensive activity of protoveratrine A and, separately, that of protoveratrine B have been studied in 13 patients given the drugs orally. Three preparations of each alkaloid have been utilized. Two consisted of the alkaloids in tablet form,‡§ prepared in different concentrations and assayed by different pharmaceutical houses by physicochemical means. The third consisted of the individual alkaloids in a liquid form‡ prepared for parenteral use. The "parenteral" preparations had been previously studied in this laboratory and found to have nearly equal hypotensive potency intravenously.[14] A mixture of protoveratrines A and B,¶ containing 53 per cent protoveratrine A ± 2 per cent, was also administered orally to 6 of these patients.

PROTOVERATRINE A		PROTOVERATRINE B
$C_{31}H_{49}O_{14}N$		$C_{31}H_{49}O_{15}N$
	Hydrolysis	
Protoverine		Protoverine
Acetic acid		Acetic acid
Acetic acid		Acetic acid
2-methyl butyric acid		2-methyl butyric acid
2-hydroxy-2-methyl butyric acid		2,3-dihydroxy-2-methyl butyric acid

FIGURE 1. *Hydrolysis of the Tetraesters, Protoveratrine A and Protoveratrine B.*

All the patients had been observed to have hypertension, either essential or renal in origin, sustained despite therapy with placebo or sedative agents. Only cases in which a hypotensive response was obtainable by oral administration of a mixture of protoveratrines A and B or of protoveratrine A alone have been included in this series. The studies were carried out in the hospital in 7, in the laboratory in 3 and in the home in 3 patients. Blood pressure and pulse rate were determined during a control period of at least twenty minutes before and during a period of hours after administration of any dose of either alkaloid. Blood pressures were measured in the sitting or semirecumbent positions by the auscultatory technic. Mean blood pressure in millimeters of mercury was calculated as the diastolic blood pressure plus one third of the difference between systolic and diastolic blood pressures.

The administration of protoveratrine A orally was initiated at doses of 0.3 to 0.5 mg. Single daily doses were raised by small increments until either a marked fall in blood pressure or the development of vomiting prohibited further increases. In the first 5 cases study of protoveratrine B was begun at similar dosage levels and with similar small increments. Thereafter, single doses of protoveratrine B were given in amounts four to ten times the hypotensive dose of protoveratrine A. The effects of multiple daily doses at intervals of six hours were also studied.

RESULTS

Protoveratrine A

Protoveratrine A by oral administration induced a definite fall in blood pressure in each patient. The onset of hypotensive activity usually occurred within

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Presented in part at a meeting of the New England Cardiovascular Society, Boston, Massachusetts, January 9, 1956.

Supported by Grant No. H1835 from the National Heart Institute, National Institutes of Health, United States Public Health Service.

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‡Kindly supplied by Kenneth Ericson, Sandoz Chemical Works, Incorporated, Hanover, New Jersey.

§Kindly supplied by Drs. Carl A. Bunde and Philip A. Boyer, Pitman-Moore Company, Indianapolis, Indiana.

¶Kindly supplied by Drs. Carl A. Bunde and Philip A. Boyer, Pitman-Moore Company, Indianapolis, Indiana.

forty-five to ninety minutes, the peak at one hundred and twenty to one hundred and eighty minutes and a return to control blood-pressure levels within four to six hours. A decrease in pulse rate attended the fall in blood pressure. The blood pressures and pulse rates shown in Table 1 represent averages of the control periods of each patient and averages of the lowest blood pressures and pulse rates in a period of hours after oral administration of each preparation of protoveratrine A. In this table only the data referable to the largest dose of drug administered to each patient are presented.

TABLE 1. *Blood Pressure and Pulse Rate before and after Oral Administration of Protoveratrine A.*

PATIENT	BEFORE THERAPY			DOSE		AFTER THERAPY			CHANGE IN MEAN BLOOD PRESSURE	CHANGE IN PULSE RATE
	SYSTOLIC-DIASTOLIC BLOOD PRESSURE	MEAN BLOOD PRESSURE	PULSE RATE	LARGEST SINGLE DOSE	EQUIVALENT	SYSTOLIC-DIASTOLIC BLOOD PRESSURE	MEAN BLOOD PRESSURE	PULSE RATE		
	mm. Hg.	*mm. Hg.*		*mg.*	*microgm./kg.*	*mm. Hg.*	*mm. Hg.*		*mm. Hg.*	
M.B.	196/122	147	86	0.75*	14	110/76	87	64	−60	−22
I.F.	198/120	146	60	0.75*	9	180/98	125	54	−21	− 6
H.H.	168/108	128		0.50*	6	124/80	95		−33	
Mean	187/117	140	73			138/85	102	59	−38	−14
A.D.	212/130	157	76	0.72†	11	190/100	130	56	−27	−20
B.K.	224/96	139	74	0.83†	15	162/70	101	64	−38	−10
Mean	218/113	148	75			176/85	116	60	−32	−15
W.R.	206/114	145	78	1.25‡	14	90/50	63	60	−82	−18
M.B.	230/138	169	94	0.63‡	12	120/100	107	66	−62	−28
A.D.	180/114	136	80	0.75‡	11	116/88	97	68	−39	−12
B.K.	194/92	126	76	0.75‡	14	174/90	118	64	− 8	−12
S.D.	192/128	149	80	0.75‡	10	130/90	103	72	−46	− 8
H.F.	180/120	140		0.50‡	6	134/96	109		−31	
M.C.	168/118	135	68	1.25‡	17	130/80	97	60	−38	− 8
R.M.	140/100	113	90	1.25‡	20	60/30	40	54	−73	−36
R.H.	160/106	124	90	1.4 ‡	13	112/70	84	68	−40	−22
F.K.	210/140	163		0.75‡	13	150/100	117		−46	
E.K.	190/100	130	68	0.75‡	10	130/50	77	66	−53	− 2
Mean	186/115	139	80			122/77	92	64	−47	−16

*Tablets supplied by Sandoz.
†"Parenteral" preparation supplied by Sandoz, given orally.
‡Tablets supplied by Pitman-Moore.

Each preparation of protoveratrine A yielded the same pattern of response. The average fall in mean blood pressure for the three preparations was 43 mm. of mercury, with a mean decrease in pulse rate of 15 beats per minute. The largest doses administered ranged from 0.50 to 1.4 mg., or 6 to 20 microgm. per kilogram of body weight.

The amount of protoveratrine A initiating hypotensive effects varied from patient to patient, but above the minimal dose, an increase in dose caused an increased effect in each patient. In this series the lowest single dose found to have hypotensive effects was 0.4 mg. The largest difference between doses that induced slight decreases in blood pressure and those causing marked hypotensive effects was 0.4 mg. In 3 of 4 patients given emetic doses, a decrease of 0.1 mg. to 0.2 mg. was sufficient to avoid the emetic effect while not interfering with the hypotensive effect.

In all but 1 of this selected group of patients, it was possible to administer protoveratrine A orally in doses that induced decreases in blood pressure without nausea or vomiting. In this case a hypotensive response was elicited only at a dose that was emetic. Side effects were common on the larger doses of protoveratrine A administered to each patient. There were 6 episodes of nausea without vomiting and 4 of vomiting. Hiccups and tightness in the chest often accompanied the vomiting. Paresthesias, most often in the mouth and throat and occasionally in the chest, extremities or genitalia, occurred in 10 patients. The paresthesias, which were described as sensations of warmth or burning and on one occasion as a coolness, were the earliest side effects, occurring at lower doses without nausea or vomiting, and were regularly present when the doses were emetic. Of note was the

lack of side effects in patient R.M., whose dose was raised until extreme hypotension occurred; when the blood pressure fell to 60 systolic, 30 diastolic, the first and only side effect, lightheadedness, developed.

Multiple daily doses of protoveratrine A were administered to 6 of these patients after a nonemetic hypotensive dose had been established in each. When equal doses were then given six hours apart, the second such dose regularly induced a greater hypotensive effect, occasionally with nausea and vomiting. Nearly equal hypotensive effects without such side effects could often be obtained if the second dose was reduced approximately 20 to 30 per cent. An example is shown in Figure 2, which also demonstrates the typical intermittency of blood-pressure and pulse responses, as induced by protoveratrine A. It is evident that cumulation of protoveratrine A occurs with oral doses six or less hours apart.

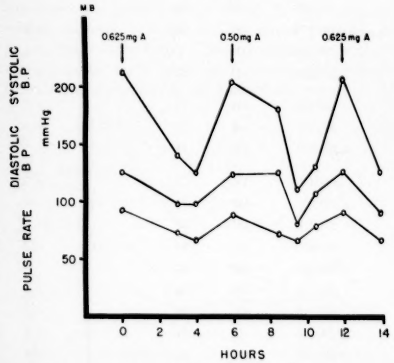

FIGURE 2. *Response to Protoveratrine A Administered Orally at Intervals of Six Hours.*

To avoid an excessive fall in blood pressure, the second dose is slightly smaller than the first. The typical intermittency of response is evident. Each point represents an average of three measurements obtained five minutes apart.

Protoveratrine B

Protoveratrine B (Table 2), in single oral doses of 1.5 to 2.0 mg. or less, did not affect the blood pressure or pulse rate. However, in the dosage range of 4.0 to 7.5 mg., or 46 to 127 microgm. per kilogram of body weight, 2 of 11 patients had striking decreases in blood pressure two or three hours after administration of the drug, with a return to previous levels within six hours. One of these patients, M.B., had been studied repeatedly on single doses of protoveratrine B of less than 4 mg. and had shown no change in blood pressure until this dose was administered. Three patients noted mild warmth or burning in the tongue and throat. There were no episodes of nausea or vomiting. The average fall in mean blood pressure after doses of 4.0 to 7.5 mg. was 9 mm. of mercury, with a mean decrease in pulse rate of 3 beats per minute.

Preliminary studies of total daily doses of more than 10 mg. of protoveratrine B have been initiated in 4 patients. These studies have shown that this agent has hypotensive potency on oral administration. The hypotensive effect in one patient was unusually prolonged, persisting for over eighteen hours. Paresthesias have occurred, but no nausea or vomiting. An unusual side effect related to neuromuscular function has been noted in 3 of the 4 patients. Because this is the first report of the behavior of this drug on oral administration in man, the details of administration and response in each patient are described.

CASE 1. M.B., a 47-year-old woman with essential hypertension of 12 years' duration, had sustained hypertension, uninfluenced by placebos or sedatives. Determinations of blood pressure and pulse rate were obtained at home at least 5 times daily for more than 2 years. On each occasion during a day 3 readings were obtained at intervals of 5 minutes. The lack of response to 2 mg. and the hypotensive response to 4 mg. of protoveratrine B are shown in Table 2.

A total dose of 17 mg. of protoveratrine B was administered in a period of 29 hours, beginning with an initial dose of 4 mg. The course of the blood pressure and pulse during the 1st 12 hours and the time and amount of drug administered are shown in Figure 3. There was an asymptomatic fall in blood pressure and pulse after each dose. However, after the last 2 doses of protoveratrine B on the following day (Fig. 4) normotension ensued and persisted for 18 hours. In the following 12 hours there was a gradual return to control hypertensive levels, but again, on the 4th morning, normotension was observed. There was a final return to control levels 44 hours after the last dose. The only side effects noted in these several days were lightheadedness and mild throat warmth. In contrast, when normotension was induced by protoveratrine A orally in this patient, nausea and vomiting occurred regularly.

In the following 3 weeks divided daily doses of 8.0 to 9.5 mg. of protoveratrine B were administered. The blood pressure and pulse rate remained sustained at control hypertensive levels, but several subjective symptoms were reported. Warmth and heaviness in the chest were noted for 30 minutes approximately 1½ hours after each dose. A "swaying sensation" when walking was described. This was not lightheadedness or vertigo but an unsteadiness in gait. The "swaying" was noted when the blood pressure was at high levels. Postural hypotension was ruled out. A sensation of "stiffness in the jaws" was also experienced.

CASE 2. S.D., a 36-year-old man with essential hypertension of 9 years' duration, was given protoveratrine B in doses of 4 mg. 3 times daily on 2 occasions several months apart.

In the 1st period of administration (5 days) there was no significant decrease of blood pressure or pulse 2 hours after each morning dose. However, the patient complained of tightness of the calf muscles on walking, heaviness of the arms and a sensation of swelling of the tongue when eating hot or cold food. Lightheadedness on awakening was noted after the 1st day of drug administration. A sensation of slight warmth in the throat, described as less intense than that after protoveratrine A, was occasionally experienced.

In the 2d period of drug administration (2 days) there were no symptoms on the 1st day and no change in blood pressure or pulse 2 hours after the 1st dose. However, a fall in mean blood pressure of 22 mm. of mercury and in pulse rate of 8 beats per minute was observed 2 hours after the morning dose on the 2d day. At this time numbness of the legs and a sensation of tightness and pain in the hips, thighs and calves were noted with walking. There was also a sensation of throat warmth. These symptoms disappeared several hours after the drug was stopped. The complaints referable to the extremities were noted only during the oral administration of protoveratrine B.

CASE 3. H.F., a 45-year-old woman with chronic glomerulonephritis, was given 4 mg. of protoveratrine B 3 times daily for a week. There were no significant changes in blood pressure, and the only side effect was warmth in the throat and mouth. Four hours after the 1st dose of 6.0 mg. the mean blood pressure fell 33 mm. of mercury, and this level was maintained for 2 additional hours. At this time she noted tightness in the throat and weakness. She described difficulty in opening the mouth to bite a sandwich and tightness of the jaw muscles. She had not previously had similar symptoms. The drug was continued for 2 days, and the dose responses were similar.

termined on at least five different days. One patient had an average fall in mean blood pressure of 41 mm. of mercury after a dose of 1.25 mg. of the mixture of protoveratrines A and B and an average fall of 35 mm. after 0.75 mg. of protoveratrine A. The falls in pulse rate were 11 and 9 beats per minute respectively. The second patient had an average fall in mean blood pressure of 28 mm. of mercury after a dose of 1.0 mg. of the mixture, and an average fall of

TABLE 2. *Blood Pressure and Pulse Rate before and after Oral Administration of Protoveratrine B.*

PATIENT	BEFORE THERAPY			DOSE		AFTER THERAPY			CHANGE IN MEAN BLOOD PRESSURE	CHANGE IN PULSE RATE
	SYSTOLIC-DIASTOLIC BLOOD PRESSURE	MEAN BLOOD PRESSURE	PULSE RATE	LARGEST SINGLE DOSE	EQUIVALENT	SYSTOLIC-DIASTOLIC BLOOD PRESSURE	MEAN BLOOD PRESSURE	PULSE RATE		
	mm. Hg.	*mm. Hg.*		*mg.*	*microgm./kg.*	*mm. Hg.*	*mm. Hg.*		*mm. Hg.*	
M.B.	210/134	159	86	2.0*	37	214/132	159	86	0	0
I.F.	210/122	151	68	1.75*	21	188/130	149	78	− 2	+10
H.H.	174/116	135		1.5*	19	154/108	123		−12	
Mean	198/124	148	77			185/123	144	82	− 4	+ 5
A.D.	214/126	155	74	1.5†	22	204/124	151	72	− 4	− 2
B.K.	218/126	157	74	2.0†	37	200/122	148	70	− 9	− 4
Mean	216/126	156	74			202/123	149	71	− 7	− 3
W.R.	216/126	156	70	5.0‡	57	208/130	156	72	0	+ 2
M.B.	216/134	161	94	4.0‡	74	150/90	110	74	−51	−20
A.D.	176/112	133	72	5.0‡	73	168/112	131	68	− 2	− 4
B.K.	164/80	108	76	4.0‡	73	180/92	121	64	+13	−12
S.D.	196/120	145	84	4.0‡	52	188/125	146	84	+ 1	0
H.F.	190/144	159	80	5.0‡	58	182/134	150	84	− 9	+ 4
M.C.	162/112	129	80	5.0‡	67	160/112	128	76	− 1	− 4
R.M.	162/100	121	90	6.0‡	94	154/100	118	94	− 3	+ 4
R.H.	164/120	135	84	5.0‡	46	164/110	128	80	− 7	− 4
F.K.	208/112	144	86	7.5‡	127	146/88	107	96	−37	+10
E.K.	220/100	140		5.0‡	67	204/94	131		− 9	
Mean	189/115	139	82			173/108	130	79	− 9	− 3

*Tablets supplied by Sandoz.
†"Parenteral" preparation, supplied by Sandoz, given orally.
‡Tablets supplied by Pitman-Moore.

CASE 4. R.H., a 33-year-old man with essential hypertension, was given protoveratrine B orally in divided daily doses of 15 mg. for 2 days. At the time of this study he had been in the hospital for 17 days. During the administration of protoveratrine B the blood pressure fell progressively to normotensive levels; 15 hours after omission of the drug, there was a return to the hypertensive state. The mean blood pressure averaged 133 mm. of mercury on the 1st and 116 mm. on the 2d day of drug administration. The mean blood pressures before and the day after administration were 146 and 143 mm. of mercury respectively. There were no side effects.

Single Alkaloids versus Mixture

A comparison of the hypotensive activity of protoveratrine A with that of protoveratrines A and B has been made in 2 patients. In each the response to a given hypotensive dose of each agent was determined on at least five different days. One patient had an average fall in mean blood pressure of 41 mm. of mercury after a dose of 1.25 mg. of the mixture of protoveratrines A and B and an average fall of 35 mm. after 0.75 mg. of protoveratrine A. The falls in pulse rate were 11 and 9 beats per minute respectively. The second patient had an average fall in mean blood pressure of 28 mm. of mercury after a dose of 1.0 mg. of the mixture, and an average fall of 26 mm. after 0.625 mg. of protoveratrine A. The decreases in pulse rate were 14 and 16 beats per minute respectively. In these patients the mean ratio of the dose of protoveratrine A to the calculated dose of protoveratrine A contained in the mixture of protoveratrines A and B to induce approximately equal hypotensive effects was 1.1.

The emetic dose of protoveratrine A was compared with that of the mixture of protoveratrines A and B in 3 other patients. The mean ratio of the emetic dose of protoveratrine A to the calculated dose of protoveratrine A contained in the emetic dose of the mixture of protoveratrines A and B was 1.1. The ratios for the individual patients were 1.1, 1.1 and 1.2.

A typical response to the oral administration of

single doses of protoveratrine A, protoveratrine B and a mixture of protoveratrines A and B is shown in Figure 5. Each agent was given on a separate day; 1.75 mg. of the mixture (containing 0.93 mg. of protoveratrine A) caused an asymptomatic blood-pressure fall to a level of 150 systolic, 90 diastolic, in two hours, and 1.25 mg. of protoveratrine A alone induced a precipitous blood-pressure fall to a level of 90 systolic, 50 diastolic, with nausea and vomiting. Both the mixture of protoveratrines A and B and the administration of protoveratrine A alone caused moderate decreases in pulse rate. After 5 mg. of protoveratrine B, there was little change in the blood pressure, and the pulse rate gradually increased.

Discussion

Veratrum alkaloids exert their hypotensive action by stimulating receptors whose impulses travel via the vagi and carotid-sinus nerves to the vasomotor center, causing a reflex fall in blood pressure and heart rate. The heart (Bezold–Jarisch effect),[15-17] carotid sinus, aortic arch and pulmonary arteries[18,19] have been implicated as the sites of the receptors that

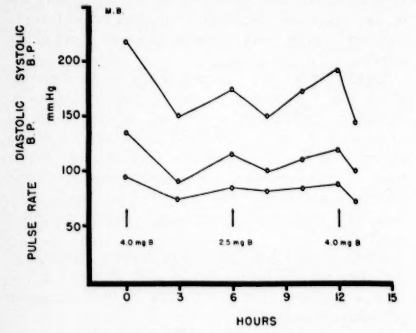

Figure 3. *Response of M.B. on the First Day of Oral Administration of Protoveratrine B in Doses of 2.5 to 4.0 Mg. Each point represents an average of three measurements five minutes apart.*

various veratrum alkaloids stimulate. There is evidence that certain veratrum alkaloids or mixtures of alkaloids may have a direct effect on the central nervous system[20,21] and that the mechanism of action of one veratrum alkaloid may differ from that of another.[22]

Protoveratrine A is a potent hypotensive agent orally. Its onset and duration of hypotensive and bradycrotic activity, its side effects of paresthesias, nausea and vomiting, the narrow dosage range between desired and undesired effects, and the evidence of cumulation of doses administered at intervals of six hours or less have also been characteristic of the activity of mixtures of protoveratrines A and B orally. However, protoveratrine A has been active orally in doses approximately half those of mixtures of nearly equal parts of protoveratrines A and B.

The "protoveratrine" that has been available to practicing physicians has been in the form of mixtures of protoveratrines A and B. The proportions of the alkaloids in such mixtures vary from one manufacturer to another and from one batch to another, with varying degrees of control by different manu-

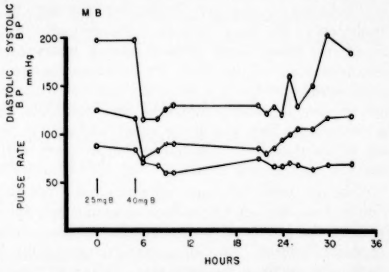

Figure 4. *Response of M.B. on the Second Day of Oral Administration of Protoveratrine B in Doses of 2.5 to 4.0 Mg. Each point represents an average of three measurements five minutes apart.*

facturers. Since protoveratrine A is the major active agent in mixtures of protoveratrines A and B orally administered, and since both protoveratrine A and mixtures of protoveratrines A and B have a narrow dosage range between hypotensive and emetic ac-

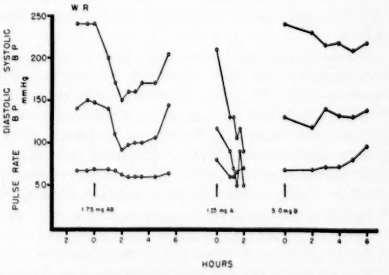

Figure 5. *Response to 1.75 Mg. of a Mixture of Protoveratrines A and B, Containing 0.93 Mg. of the Former, to 1.25 Mg. of Protoveratrine A, and to 5.0 Mg. of Protoveratrine B Administered Orally on Separate Days to W.R., a Forty-five-Year-Old Man with Malignant Hypertension.*

tivities, variations in the proportions of the alkaloids in mixtures would account for some variations in response. Hence, the substitution of protoveratrine A for mixtures of protoveratrines A and B appears desirable and would eliminate one factor influencing the variability of response to oral "protoveratrine" therapy.

Preliminary studies of protoveratrine B in doses of more than 10 mg. a day by mouth have indicated that this alkaloid can have hypotensive effects by the oral route. The prolonged normotension, observed in 1 of the 4 patients to whom doses of this size were administered, is of interest, as is the progressive fall in blood pressure to normal levels in a second patient. Although emetic activity has not yet been encountered, an unusual side effect related to neuromuscular function has appeared in 3 of these 4 patients — that is, "tightness of the calf, thigh and hip muscles," "tightness of the jaws" and an unsteady gait. These symptoms disappeared within several hours after discontinuation of the drug. In 1 patient the symptoms were reproduced when the drug was readministered several months after the first period of administration. The symptoms appear related to the size of the dose but unrelated to the presence or absence of hypotensive effects.

Although pure veratrum alkaloids have not previously been known to produce muscular symptoms in man, the effects of veratrum alkaloids on neuromuscular function have been studied extensively in the laboratory for a hundred years. Much of the research has been concerned with nerve or muscle response to veratrine,[10] the mixture of veratrum alkaloids obtained from the seeds of *Schoenocaulon officinale*. Veratrine renders nerve and skeletal muscle capable of responding to brief stimuli in a prolonged manner. The tissues exhibit a repetitive response, consisting of a series of all-or-none impulses, which long outlasts the stimulus. The veratrine response is strikingly like the muscular response in myotonia congenita and dystrophia myotonica. The muscular symptoms induced by protoveratrine B suggest those of myotonia.

Obvious muscular effects have not been observed after small hypotensive doses of protoveratrine B intravenously. The muscular symptoms that have followed large but not necessarily hypotensive doses of this agent orally may be related to the size of the dose, although the possibility exists that this alkaloid undergoes conversion within the alimentary canal to another substance with strong neuromuscular activity.

By the intravenous route protoveratrine A or protoveratrine B can induce hypotensive effects in doses of 0.1 to 0.25 mg.[23] Since orally doses of more than three times this amount have been required for protoveratrine A and more than thirty times for protoveratrine B to initiate lowering of the blood pressure, it is evident that these alkaloids are either incompletely absorbed or rapidly inactivated in the gastrointestinal tract or liver (protoveratrine B to a much greater extent than protoveratrine A). Hydrolysis of either ester is known to yield the alkamine, protoverine. This alkamine is devoid of hypotensive activity.[24]

Further studies of pure veratrum alkaloids by intravenous and oral routes are indicated and are in progress. Additional observations of the hypotensive and neuromuscular effects of protoveratrine B are planned, including studies to determine whether the muscular effects may be opposed by quinine or procaine amide, agents that have antagonized clinical myotonia[25,26] and, for quinine, the veratrine response.[27]

Wyss and Spühler,[28] who were aware of these studies, have since confirmed the quantitative difference between protoveratrine A and protoveratrine B given orally.

Summary and Conclusions

An unequivocal quantitative difference in hypotensive activity has been established between protoveratrine A and protoveratrine B when the substances are administered orally. Protoveratrine A is a potent hypotensive agent with a narrow therapeutic dosage range. It is the major active principle in mixtures of protoveratrines A and B administered by mouth. The use of protoveratrine A instead of a mixture of protoveratrines A and B would remove one factor affecting the variability of response to oral protoveratrine therapy. Nonetheless, the satisfactory use of any veratrum preparation requires critical attention to dosage and consideration of cumulative effects.

Protoveratrine B is inactive orally in doses several times the hypotensive doses of protoveratrine A. However, preliminary studies of divided doses of more than 10 mg. a day have indicated that protoveratrine B has strong hypotensive activity, which may be prolonged and not accompanied by emetic effects. Unusual side effects related to muscle function have appeared, resembling clinical myotonic syndromes.

These studies have provided definite evidence of the value of the use of single pure alkaloids rather than a mixture. Further studies of pure veratrum alkaloids are indicated.

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CIRRHOSIS AND PRIMARY CARCINOMA OF THE LIVER*

Changes in Their Occurrence at the Boston City Hospital, 1897-1954

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OCCASIONAL reports of a high incidence of primary carcinoma of the liver have appeared in the American medical literature in recent years. These observations have not in general received a great deal of attention, owing at least in part to the fact that the number of cases of carcinoma in such reports has been small. During the course of a review of biliary-system neoplasms at this hospital it was noted that the number of primary carcinomas of the liver, both hepatomas and cholangiomas, had significantly increased during the past eight years. Whereas the incidence in 15,491 autopsies during the years 1917 through 1946 was 0.34 per cent, a figure in agreement with most reports from this country, the incidence in 7623 autopsies during the years 1947 through 1954 was 0.72 per cent. The study with which this paper is concerned was undertaken in an attempt to obtain information concerning this increase.

REVIEW

Early reports of the incidence of primary carcinoma of the liver made from different parts of the United States varied considerably, but the figures presented were generally low. In 1923 Clawson and Cabot,[1] in Minnesota, reported 1 case in 5100 autopsies, or 0.02 per cent. Fried,[2] in 1924, reported from the Peter Bent Brigham Hospital in Boston that 4 cases had been found in 1200 autopsies, or 0.33 per cent. Two years later Counsellor and McIndoe[3] found 5 cases in 5976 autopsies at the Mayo Clinic, or 0.08 per cent. Fox and Bartels,[4] in Iowa, cited an incidence of 0.13 per cent in 1500 autopsies. Mallory[5] found 12 cases in 9346 autopsies during the years 1897 to 1932 at the Boston City Hospital, an incidence of 0.13 per cent; he noted, however, that nearly a quarter of the autopsies had been performed on children with infectious diseases. Another publication in 1932, by Rosenthal,[6] at the Cook County Hospital in Chicago, observed an incidence of 0.57 per cent in 2091 autopsies. Brines,[7] at the Detroit Receiving Hospital, recorded 8 cases, or 0.74 per cent, in 1087 autopsies. In 1937 Gustafson[8] reported from Bellevue Hospital in New York City that 62 cases had occurred in 24,400 autopsies, an incidence of 0.25 per cent. Berman[9] summarized 20 reports from North America up to 1943 as averaging 0.27 per cent in 108,632 autopsies.

One of the early observations of a possible change in incidence figures was noted in 1937, when Lynch,[10] in Charleston, South Carolina, compared the autopsies of two periods regarding carcinoma of the liver and healed acute yellow atrophy. In 1428 autopsies before 1928 he found no cases of either disease, whereas in 1529 autopsies performed after 1928 he found 11 cases of healed acute yellow atrophy and 6 cases of carcinoma. All but 1 of the cases of carcinoma were in livers with healed acute yellow atrophy. It is to be noted that Lynch was reporting from a hospital service where the autopsy population was almost entirely made up of Negroes. Collenberg,[10] in his discussion that followed the presentation of this paper, reported that he had reviewed cases of carcinoma of the liver at Baltimore hospitals and that he had not made observations concerning healed acute yellow atrophy such as Lynch had presented. He had, however, observed an increase in the incidence of hepatic carcinoma at the Johns Hopkins Hospital from 0.07 per cent of autopsies during the years 1900 to 1925, to 0.24 per cent during the years 1925 up to 1933. Subsequent authors also presented evidence of an increase. Holley and Pierson,[11] in 1948, in Birmingham, Alabama, found 5 cases of carcinoma in 500 consecutive autopsies, or

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1 per cent. In 1952 Schupbach and Chappell[12] reported from the Veterans Administration Hospital in Memphis, Tennessee, that in 797 autopsies performed since 1946, they had found 14 cases, or 1.76 per cent. Among factors to be considered in the reports described above are the small number of cases with which each worker was dealing and the selection of hospital populations, as in Lynch's paper and in that of Schupbach and Chappell. In none of the later reports except that of Lynch were sufficient data available to permit the authors to determine the factors responsible for the high incidence that they were observing.

rent use, and for diagnoses that were considered equivocal by the original examiner. In cases in which these were found the microscopical sections were reviewed in an attempt to answer such questions. In the study of the tumors microscopical sections of 47 of 80 hepatomas, of 4 hepatocholangiomas and of 15 of 24 cholangiomas were available, and these were reviewed. The remaining cases included in this report were accepted as valid from a study of the gross and microscopical descriptions made at the time of autopsy.

Because of the high association of carcinoma with cirrhosis, all cases of the 7 types of cirrhosis as diag-

TABLE 1. *Incidence of Primary Carcinoma of the Liver in Seven Types of Cirrhosis.*

TYPE OF CIRRHOSIS	PRESENT STUDY (38 YR.)			MALLORY[5] STUDY IN 1932 (35 YR.)		
	NO. OF CASES OF CIRRHOSIS	NO. OF CASES OF CARCINOMA	OCCURRENCE IN CIRRHOSIS	NO. OF CASES OF CIRRHOSIS	NO. OF CASES OF CARCINOMA	OCCURRENCE IN CIRRHOSIS
			%			%
Healed acute yellow atrophy	222*	29†	13.1	46	3	6.5
Hemochromatosis	155‡	12§	7.7	49	4	8.2
Fatty nutritional	1069	26	2.4	270	3	1.1
Undetermined	378	8	2.1	104	1	1.0
Biliary	340¶	7	2.1	52	1	1.9
Cardiac	202	0	0	—	—	—
Syphilitic	36	0	0	28	0	0
Totals	2402	82		549	12	
Averages			3.4			2.2

*In 28 cases alcoholic (fatty nutritional) cirrhosis also present.
†In 1 case alcoholic (fatty nutritional) cirrhosis also present.
‡In 15 cases alcoholic (fatty nutritional) cirrhosis also present.
§In 2 cases alcoholic (fatty nutritional) cirrhosis also present.
¶In 10 cases alcoholic (fatty nutritional) cirrhosis also present.

MATERIALS AND METHODS

This study is concerned with primary liver-cell carcinomas (hepatomas), with carcinomas of intrahepatic-bile-duct origin (cholangiomas) and with tumors showing both elements of growth, or hepatocholangiomas.

For a consideration of the autopsy findings during the years 1897 to 1932 the study of cirrhosis and primary carcinoma of the liver made at this hospital by Mallory[5] in 1932 was reviewed. The present report, beginning with the year 1917, overlaps the latter period of his study. The number of autopsies performed at this hospital during the years 1917 through 1954 was 23,114; among this number were 108 cases of primary hepatic carcinoma. In the review of the total autopsies, the written microscopical diagnoses from each case were reviewed individually. In addition the complete gross and microscopical descriptions of the 7805 autopsies performed between the years 1917 and 1936 were individually reviewed. A search was made in the latter cases for diagnostic criteria that might have differed from those in current use, and for diagnoses that were considered equivocal by the original examiner. In cases in which these were found the microscopical sections were reviewed in an attempt to answer such questions. In the study of the tumors microscopical sections of 47 of 80 hepatomas, of 4 hepatocholangiomas and of 15 of 24 cholangiomas were available, and these were reviewed. The remaining cases included in this report were accepted as valid from a study of the gross and microscopical descriptions made at the time of autopsy.

Because of the high association of carcinoma with cirrhosis, all cases of the 7 types of cirrhosis as diagnosed microscopically were tabulated. The written protocols of the cases of healed acute yellow atrophy, of hemochromatosis and of fatty nutritional cirrhosis were reviewed as a check on the consistent use of diagnostic terms. The terminology in use at this institute for the microscopical diagnoses of hepatic disease are in general agreement with the interpretation of most pathologists. Slight variations, however, may be found in the use of some terms. Fatty nutritional cirrhosis includes such conditions as portal cirrhosis, Laënnec's cirrhosis and alcoholic cirrhosis. Hemochromatosis is perhaps applied in a more specific manner than is used generally: in addition to the finding of hemosiderin deposits in a cirrhotic liver, in the pancreas and in endocrine organs, hemofuscin pigment must be demonstrated in the liver or in one of the affected organs. Healed acute yellow atrophy includes such diagnoses as toxic cirrhosis and postnecrotic cirrhosis, and biliary cirrhosis such forms as cholangiolitic cirrhosis and infectious cirrhosis. Cirrhosis of undetermined type is applied in cases in which the cirrhotic changes are so marked or so atypical that the manner in which the process de-

veloped, or its etiology, cannot be evaluated, and in cases in which a slight portal type of cirrhosis is found but definite criteria for the diagnosis of fatty nutritional cirrhosis are lacking.

Results

During the years 1917 through 1954, of 108 primary carcinomas of the liver found in autopsies, 82, or 75.9 per cent, were associated with cirrhosis. This association is summarized in Table 1; the earlier figures reported by Mallory[5] in 1932 are also summarized. Of 84 hepatomas (including the 4 hepatocholangiomas in this group) 72, or 85.7 per cent, were associated with cirrhosis, whereas only 10 of the 24 cholangiomas, or 41.7 per cent, were associated with cirrhosis. The rate of occurrence in all types of cirrhosis was 3.4 per cent in the present study, contrasted with 2.2 per cent in the earlier report. The strikingly high association of carcinoma with healed acute yellow atrophy, 13.1 per cent, was far greater than that for other types of cirrhosis. In Mallory's study the type of cirrhosis most frequently associated with carcinoma was hemochromatosis, although healed acute yellow atrophy was also frequent. In the present study hemochromatosis had nearly the same relation to carcinoma as that found by Mallory, 7.7 per cent, as compared with 8.2 per cent, but it now stands second in types of cirrhosis with associated carcinoma, owing to the present high rate of carcinoma in healed acute yellow atrophy.

Table 2 summarizes the occurrence of cirrhosis in various periods during the thirty-eight years covered in the present study. The incidence of cirrhosis in autopsies was relatively constant until the period 1947-1954, when it increased from an average in the thirty previous years of 8.65 per cent to 13.93 per cent; during these eight years nearly as many cases of cirrhosis were found as during the entire thirty previous years. Cardiac cirrhosis and hemochromatosis did not contribute to this increase. Syphilitic cirrhosis, as might be expected, decreased to the point where it is now an extremely rare autopsy finding. The three types of cirrhosis that underwent statistically significant increases in occurrence were healed acute yellow atrophy, fatty nutritional cirrhosis and the undetermined type. Of these, the first two were most important to this study, because of their association with carcinoma of the liver. Healed acute yellow atrophy was found in 0.49 per cent of autopsies during the years of Mallory's[5] study and in 0.96 per cent of autopsies during the years of the present study; in the most recent period, 1947-1954, it was found in 1.40 per cent of autopsies.

Table 3 summarizes changes in the occurrence of carcinoma of the liver in five types of cirrhosis. Corresponding with the increase in cases of cirrhosis, more cases of carcinoma were found in the eight years from 1947 to 1954 than in the thirty previous years. This increase was chiefly due to the increase in the number of tumors accompanying healed acute yellow atrophy and fatty nutritional cirrhosis, and in part to an increased number of cases without underlying cirrhosis. As emphasized below, the incidence of carcinoma developing in livers with healed acute yellow atrophy and fatty nutritional cirrhosis did not change significantly.

Table 2. *Occurrence of 2402 Cases of Cirrhosis in 23,114 Consecutive Autopsies, 1917-1954.*

Type of Cirrhosis	No. of Cases in 1917-26	No. of Cases in 1927-36	No. of Cases in 1937-46	No. of Cases in 1947-54	Totals
Fatty nutritional	56	194	243	576	1069
Undetermined	31	139	54	154	378
Biliary	15	64	153	108	340
Healed yellow atrophy	16	44	45	117	222
Cardiac	20	70	44	68	202
Hemochromatosis	31	44	43	37	155
Syphilitic	11	19	4	2	36
Totals	180	574	586	1062	2402
No. of autopsies	2055	5760	7676	7623	23,114
Incidence of cirrhosis in autopsies	8.76%	9.97%	7.63%	13.93%	10.39%

Discussion

A statistical analysis of the data of this study indicates that the increased number of cases of primary carcinoma of the liver, of healed acute yellow atrophy and of fatty nutritional cirrhosis during the years 1947-1954 is significant beyond the 1 per cent level. The increase in cases of carcinoma without underlying cirrhosis, however, including 2 cases in children referred to below, approximates but does not reach the 5 per cent level of significance. Some of the factors that appear to contribute to these increases are briefly mentioned below.

The most generally accepted concept of the pathogenesis of primary carcinoma of the liver is that these tumors usually develop in livers with pre-existing cirrhosis. Exceptions are the tumors found in infants and children, since cirrhosis is only rarely present in such cases.[13] This concept is pertinent to an evaluation of the data presented in this report, for the increased number of cases of hepatic carcinoma in recent years appears to be due chiefly to three factors: an increase in carcinoma paralleling an increase in cases of healed acute yellow atrophy; a similar parallel increase accompanying an increase in cases of fatty nutritional cirrhosis; and a slight increase in the number of cases of carcinoma developing in patients without cirrhosis. As seen from Table 3 the incidence of neoplasm in these two types of cirrhosis did not undergo a significant increase, so that the large number of cases of carcinoma in these two diseases re-

flected only an increase in their total number. The important questions arising from these observations thus concern an explanation not only for the increase in the number of cases of carcinoma in recent years but also for the increase in occurrence of these types of cirrhosis.

since hepatitis is more severe in persons with poor nutrition and in pregnant women.[24] The finding, in this and in Lynch's[10] study, that healed acute yellow atrophy is associated with an unusually high incidence of liver carcinoma raises provocative questions concerning the etiology of this type of cirrhosis.

TABLE 3. *Occurrence of Primary Carcinoma of the Liver in Five Types of Cirrhosis during the Years 1917 through 1954.*

PERIOD	NO. OF AUTOPSIES	PRIMARY CARCINOMAS	CASES OF HEALED YELLOW ATROPHY	PRIMARY CARCINOMAS	CASES OF FATTY NUTRITIONAL CIRRHOSIS	PRIMARY CARCINOMAS	CASES OF HEMOCHROMATOSIS
1917-26	2055	9(0.44%)	16	1(6.25%)	56	2(3.57%)	31
1927-36	5760	22(0.38%)	44	7(15.91%)	194	2(1.03%)	44
1937-46	7676	22(0.29%)	45	3(6.66%)	243	5(2.06%)	43
1947-54	7623	55(0.72%)	117	18(15.38%)	576	17(2.95%)	37

The finding of an increasingly aging population appears to be one important factor. The use of age-specific death rates and age-adjusted ratios in calculations accounts for approximately a third of the increment in carcinoma of the liver observed during the period 1947-1954. Similarly, it accounts for a third of the increase in healed acute yellow atrophy and fatty nutritional cirrhosis. Age may also be a factor in patients in whom carcinoma of the liver develops without underlying cirrhosis. Of 13 such patients during the years 1947-1954, 2 were children, — the only 2 in the entire series of carcinoma of the liver, — and their occurrence during these years may have been due to chance alone. One other patient was a thirty-six-year-old man who had both a primary liver-cell carcinoma without underlying cirrhosis and an early unsuspected carcinoma in a sigmoid polyp; the remaining patients had an average age of seventy years. It has been pointed out in the past that with increased longevity more people live to manifest neoplasms; the liver may be one site in which tumors develop more frequently with advancing age. The increase in fatty nutritional cirrhosis raises interesting sociologic questions in that excessive use of potent alcoholic beverages coupled with poor dietary intake is considered to be the most important etiologic factor in cases of this type of cirrhosis seen at this hospital. The question of etiology in healed acute yellow atrophy is probably not related to a single factor, although hepatitis, both the infectious and the homologous-serum form, is implicated as an etiologic agent. There is accumulating evidence that this is true.[14-21] Older concepts that metals and toxins are the important factors in producing this type of liver disease remain to be evaluated in the light of newer information concerning the transmissibility and frequency of viral hepatitis.[22] The experimental work of Himsworth and Glynn,[23] who succeeded in producing cirrhosis of the healed-acute-yellow-atrophy type with diets deficient in protein, may have bearing on this problem,

SUMMARY AND CONCLUSIONS

A review of autopsied cases of cirrhosis and primary carcinoma of the liver at the Boston City Hospital during the years 1917 through 1954 is presented. The findings of this study are compared with an earlier report from this hospital covering the years 1897 to 1932.

An increase in cases of primary hepatic carcinoma during the years 1947-1954 is chiefly ascribed to three factors: an increase in cases of healed acute yellow atrophy, and of fatty nutritional cirrhosis, both types of cirrhosis being consistently accompanied by carcinoma, and to a lesser extent to an increased number of cases of carcinoma developing in adult patients without cirrhosis.

Some of the factors contributing to the increase in healed acute yellow atrophy, of fatty nutritional cirrhosis and of carcinoma without underlying cirrhosis are mentioned. One factor in common to all groups is increased longevity in recent years. A rise in the use of alcoholic beverages coupled with poor dietary intake is possibly of importance in the increase in cases of fatty nutritional cirrhosis, and viral hepatitis is considered to be an important factor in the etiology of healed acute yellow atrophy.

Attention is called to a high incidence of carcinoma of the liver in patients with healed acute yellow atrophy. The need for further studies of this type of cirrhosis is emphasized.

I am indebted to Drs. G. Kenneth Mallory and Stanley L. Robbins for continued assistance and suggestions during the course of this study.

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TABLE 3 *(Concluded).*

PERIOD	PRIMARY CARCINOMAS	CASES OF UNDETERMINED TYPE OF CIRRHOSIS	PRIMARY CARCINOMAS	CASES OF BILIARY CIRRHOSIS	PRIMARY CARCINOMAS	CASES OF CARCINOMA WITHOUT UNDERLYING CIRRHOSIS	AVERAGE AGE AT DEATH OF PATIENTS WITH CARCINOMA
1917-26	3(9.67%)	31	1(3.23%)	15	0	2	57.9
1927-36	2(4.55%)	139	3(2.16%)	64	3(4.69%)	5	60.3
1937-46	3(6.98%)	54	2(3.70%)	153	3(1.96%)	6	66.0
1947-54	4(10.81%)	154	2(1.30%)	108	1(0.93%)	13	65.6*

*Excluding 2 patients <17 yr. of age.

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THE NATURAL HISTORY OF PREDIABETES*

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YEARS before a woman becomes overtly diabetic she may produce babies who are large and who are often stillborn or die in the neonatal period.[1-3] Such babies show specific abnormalities, especially of the pancreas. The underlying state of these women, destined later to become diabetic, is called "prediabetes." The patient in the case reported below represents to us the personification of prediabetes.

Mrs. S. is an intelligent 38-year-old colored woman, a nurseryman's wife, weighing 97.5 kg. (215 pounds). Her mother was diabetic. Before the birth of her 1st child she was slim, but her weight progressively increased with each of her 1st 4 pregnancies. The birth weights of her babies also increased; the 1st 7 were born alive, and their weights ranged from 4.1 to 5.0 kg. (9 to 11 pounds). Then came a stillborn infant weighing 5.1 kg. (11 pounds, 2 ounces) delivered at term. The next infant, which was 4 weeks premature but weighed 4.2 kg. (9 pounds, 4 ounces), died in the neonatal period (Fig. 1). Microscopical examination of this infant's pancreas some 2 years later revealed grossly enlarged islands of Langerhans, as discussed below (Fig. 2), and the liver showed excessive extramedullary hematopoiesis (Fig. 3).

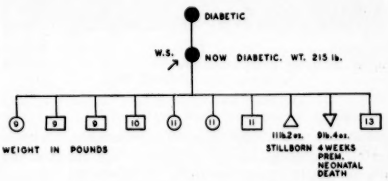

FIGURE 1. *Family Tree of Mrs. S.*
The blacked-in portions indicate persons with diabetes, and the triangles death in the perinatal period.

We first saw Mrs. S. in her next and most recent pregnancy and suspected prediabetes from her history although sugar had not been found in her urine during any of her pregnancies. A glucose tolerance curve (50 gm. of glucose orally, by the Hagedorn–Jensen estimation) at 8 months showed elevation of the 2-

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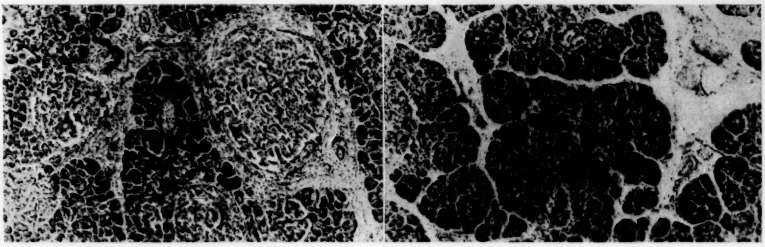
hour and 2½-hour blood sugar levels (Fig. 4), a feature that is characteristic of the "prediabetic" curve.[2] Cesarean section was performed before term; yet the infant weighed 5.9 kg. (13 pounds) and was fat, flabby, rubicund, edematous and markedly "Cushingoid" in appearance (Fig. 5). The management of this child was the same as that given at this hospital to the baby of an established diabetic patient (oxygen tent, starvation for 48 hours, stomach washouts and so forth). This child lived and is now healthy at 2 years of age.



A B

FIGURE 2. *Typical Fields of the Pancreas (Low-Power Views) of the Patient's Stillborn Child* (A) *and of the Stillborn Child of a Nondiabetic Mother* (B).
Note the hypertrophy and hyperplasia of the islets in A.

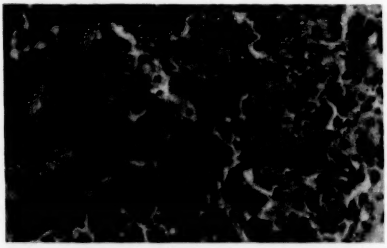


FIGURE 3. *Section of the Liver of the Patient's Stillborn Infant, Showing Extramedullary Hematopoiesis (Hematoxylin and Eosin Stain X270).*

In the puerperium (after the "stress" of pregnancy was over) the patient's glucose tolerance curve reverted to normal, but on retesting some months later it was again abnormal in a "prediabetic" manner. Now, after another 2 years, she has gross glycosuria and a fully diabetic tolerance curve (Fig. 4) though so far she is free of symptoms.

PANCREAS OF STILLBORN INFANT

On examination of the pancreas of the stillborn infant the islands of Langerhans were extraordinarily hypertrophied (Fig. 2) — more like "continents" of Langerhans. Using a method of measurement that we intend to describe in a later publication, we estimated that islet tissue comprised 13.6 per cent of the total pancreas, whereas the mean percentage of islet tissue in a large series of stillbirths from other causes was 1.3. Furthermore, use of the Wilson–Gömöri aldehyde-fuchsin stain showed that the beta cells in the islets were in the unusually high proportion of 80 per cent of all cells (normal, about 40 per cent). Finally, the beta cells in this pancreas were crammed full of granules — certainly twice the number usually seen in stillbirths. Simple arithmetic indicates that sections of this pancreas contained roughly 36 times as many beta-cell granules as the number found in the normal organ. According to Hartroft

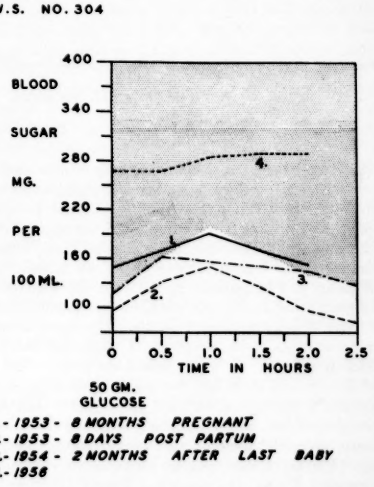


FIGURE 4. *Glucose Tolerance Curves of Mrs. S.*

and Wrenshall[4] the degree of beta-cell granularity is proportional to the content of extractable insulin of the pancreas. On this basis the extractable insulin of this infant's pancreas would parallel the striking increase in beta granules and would thus be elevated many times above the normal.

The liver of this infant showed very active extramedullary hematopoiesis (Fig. 3), almost indistinguishable from that seen in cases of erythroblastosis fetalis.

Discussion

The family history of diabetes, the repeated stillbirths and the large size of the babies made us suspect prediabetes very strongly in this patient, despite the absence of glycosuria in pregnancy. We believed that the slight abnormality in the glucose tolerance curve

FIGURE 5. *Patient's Last Baby (on the Left), Weighing 5.9 Kg. (13 Pounds) at Birth, Compared with a Normal Child, Weighing 2.9 Kg. (6 Pounds, 8 Ounces). Note the fat, flabby, edematous, congested, "Cushingoid" appearance of the infant of the mother with prediabetes.*

was confirmatory evidence. We have learned that high figures at two and two and a half hours (over 140 and 130 mg. per 100 ml., respectively) are very significant in a test performed late in pregnancy, or on about the sixth post-partum day.

It was a surprise to find such a degree of pancreatic-islet hypertrophy, although it is well known that the stillborn infants of diabetic mothers show this phenomenon.[5,6] Van Beek[7] has claimed, and we have confirmed, that stillborn infants of *prediabetic* mothers can also have islet hypertrophy — to a greater extent in some cases than the babies of patients with established diabetes. This suggests that something is producing gross stimulation of islet activity and insulin production in the fetus of a prediabetic mother. The mechanism is apparently not maternal hyperglycemia.

Conclusions

By recognizing prediabetes in Mrs. S. we believe that we were able to save her last baby's life. Cesarean section was performed before term, and yet the baby weighed 5.9 kg. (13 pounds) and after birth behaved very much as a delicate premature child; it was managed as such.

Mrs. S. is at present free of symptoms. By diagnosing her diabetes in this stage we hope to be able to control it completely by dietary measures, and perhaps the final episode in the story will be a return to normal glucose tolerance after loss of some 18 kg. (40 pounds) in weight.

We should therefore suspect prediabetes as the cause of any unexplained stillbirth, and test for this by determining glucose tolerance and examining the pancreas of the newborn infant. It is strange that we may confidently make the diagnosis of a disease in the mother, which may not be manifest for years, by examining the tissues of her child.

This case does not stand alone. It illustrates very well the natural history of prediabetes; the story is mirrored in many other cases.

We are indebted to Professors J. E. Brock, F. Forman, J. G. Thomson, G. C. Linder and J. T. Louw, Drs. T. Sacks and R. Hoffenberg and our technicians for co-operation and assistance. We are in receipt of a grant from the University of Cape Town Staff Research Fund.

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MEDICAL PROGRESS

HUMAN INFERTILITY (Concluded)

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RESEARCH IN INFERTILITY

This review will not consider in detail advances in research in infertility or proposals toward such investigations. These are admirably covered by a recent publication (1955) sponsored by the American Foundation of New York and Westbrook, Connecticut, entitled "Medical Research: A mid-century survey." In the second volume, under the title, "Unsolved Clinical Problems, in Biological Perspective," pages 135 through 192 discuss infertility resulting from defects in the female or male reproductive cycle or both. Provocative, detailed and inclusive, covering not only barriers to conception but also anything that prevents production of a normal child capable of continued growth and development, including spontaneous abortion, premature birth, stillbirth, neonatal death and congenital anomaly, this survey is recommended to all interested in the challenge of these problems.

In a similar vein, it seems unnecessary to review again the vast amount of current opinion so ably presented by various articles available in the last year, except to comment editorially perhaps.

Clinical Evaluation of Testicular Biopsy and the Rebound Phenomenon

Only 3 of 104 physicians recently canvassed routinely ordered testicular biopsy in the medical investigation of male sterility. (Biopsy is *not* a routine; 65 of those canvassed employed it in cases of azoospermia and oligospermia in which it is of value and to which it is normally restricted.)

Although it is admitted that testicular biopsy is a diagnostic aid, properly obtained, fixed and interpreted, it allows one to predict with reasonable accuracy the future fertility or lack of it of the given male. For example, in 20 consecutive men at the Massachusetts General Hospital who had oligospermia or azoospermia who did not respond to routine medical therapy, the biopsy unequivocally showed "arrest of spermatogenesis." None of these men have had children. Therefore, it might be argued that proper biopsy settles the question of irrevocable sterility thus far. No one will deny that one of the functions of the consulted physician is to help the infertile partners to learn their prognosis. It is just as important for physicians to advise the infertile couple when to give up investigation and treatment as it is to correct their barren state. This advice should be withheld, of course, until all reasonable diagnostic and therapeutic efforts have been exhausted.

Even a few spermatozoa were found in the semen of 18 men whose biopsy revealed "absence of germ cells." It seems futile to attempt to treat a man with no germ cells. Restoration of such damaged tubules by treatment is impossible, according to Howard, Sniffen and Simmons: in a group of 109 adults with diagnoses of interstitial fibrosis, absence of germ cells, arrest of maturation in spermatogenesis, and unexplained oligospermia with normal testes, there was no improvement under endocrine therapy, and there were no children.

These patients can be advised at once to abandon treatment and hope; yet they may choose therapeutic insemination or adoption while the wife is young enough to conceive or adopt.

Sixty-four clinicians furnished at least 20 different definitions of oligospermia, varying from 1,000,000 to 70,000,000 spermatozoa per milliliter. Regarding some men as infertile because they have relatively low sperm counts (20,000,000 to 40,000,000 per milliliter) ignores the fact that such males have been demonstrated to be in reality fertile.

Here, indeed, is the crux of the matter. Despite the availability of more than a dozen textbooks on human infertility in the past decade and, since 1950, 208 infertility articles abstracted in the *Yearbook of Obstetrics and Gynecology,* the apathy of the medical profession persists in ignoring definition. Clinicians either do not read or refuse to overcome their prejudices regarding what sterility is. Sad is the state of the couple superficially branded as sterile by the man who applies the knowledge of the preceding decade to the patients of this decade. Worse, perhaps, is the predicament of the couple who are told that there is no reason why they cannot have children when all the examination they have had is a pelvic examination of the wife or study of one semen specimen from her mate. This plight exists in the problem of one-child sterility as well. Often the well meaning obstetrician withholds uterotubal insufflation from his patient who has had one delivery when in fact it is a complication of that pregnancy that has partially agglutinated the tubal lumens or blocked them. I suggest that today the most important therapy for the moderately infertile husband who is not irrevocably sterile is to improve the fertility of his spouse by insufflation, uterotubogram, thyroid or hygiene — even to the extent of surgery on the female generative tract (the various technics are referred to below in the section entitled "Surgery").

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The conception rate with testosterone therapy was less than 4 per cent. Of 840 cases treated there were 56 conceptions.

Unfortunately for the equivocally labelled oligospermic male, clinicians failed to note that in 1950 Heller, in the discussion of the new "testosterone-rebound" phenomenon introduced by him and his co-workers, pointed out that their results *did not constitute suggestions for definitive treatment.* Heckel has regularly reported marked improvement in oligospermic males after testosterone in large doses. But his criterion of oligospermia is far above that now well established as definitive by MacLeod and other experts. Authorities on testosterone and its hazards (Hotchkiss, MacLeod, Dorfman, Simmons, Getzoff and Salmon) view with skepticism this therapeutic trial. It may cause irreversible damage, according to Dorfman, MacLeod and Charny. Certainly, no male should have such a large dose of testosterone without adequate urinalysis for gonadotrophins and 17-ketosteroids and testicular biopsy.

Treatment of the Male

There is scant indication for treatment of the infertile male with male hormone: testosterone actually causes a decrease in spermatogenesis except in isolated cases. Except for azoospermia, the adoption of simple health measures constitutes the best therapy. Even if the semen specimen is over 20,000,000 per milliliter, with good motility, the male in question should be advised to avoid excessive use of alcohol, nicotine and caffeine, as well as sexual excesses. He is encouraged to get regular hours of adequate sleep, outdoor exercise and work. Diet should include an adequate protein and vitamin intake. Despite the thyroid myth of Tyler the husband may well improve his fertility by adequate doses of desiccated-thyroid pills given by mouth under supervision. In this busy hurly-burly world, he must plan adequate vacation from business and social responsibility, and even from family responsibility. In the event of hyperthermia of the scrotum or testes, he must abandon skintight underwear, jockey shorts, suspensories and the like. Large varicoceles should be repaired. Taxicab drivers, truck drivers and traveling salesmen and others who may spend long hours behind the steering wheel of modern vehicles must not overdress, must avoid the use of a heater and must occasionally ventilate themselves from the noxious influences of carbon monoxide gas and ethyl fumes. Occasionally (and only occasionally), subfertile males may benefit from the judicious use of gonadotrophic or androgenic hormone. Despite the elaborate literature and claims of well meaning detail men, the administration of hormones to the male (or female, for that matter) is repetitively disappointing. Almost all textbooks and papers from the teaching clinics decry the promiscuous use of hormones in infertility unless there is a specific glandular disorder. This is not true, however, in habitual abortion, but even here the best time to treat is before conception, both husband and wife.

The conservative approach of Sturgis will perhaps put the quietus on current indiscriminate hormonotherapy. He says, "Recent work on the 'rebound phenomenon' after testosterone therapy in some oligospermic males suggests that this may be *of no more value than other* endocrine regimes to enhance male [or female] fertility."

Surgically, the subfertile male may benefit from testicular biopsy, epididymovasostomy, irrigation of the ductus deferens, catheterization of the ejaculatory ducts and repair of large varicoceles, hydroceles and spermatoceles and, of course, surgical repair of incomplete descent of the testes before puberty and of large hernias. It is not generally known that divided vasa deferentia can be surgically repaired with over 50 per cent salvage, as pointed out by Vincent J. O'Connor at the first World Congress on Fertility and Sterility in 1953. Whereas the usually optimistic Buxton, in a critical review in June of this year, pessimistically stated there is only a 4 per cent chance of subsequent sperm ejaculation after epididymovasostomy, Bayle, the French exponent of definitive surgical attack, reports 66 cures in 95 favorable cases, with 45 actual births. In proper hands and with selected cases, the physician may predict relief of obstructive epididymitis in about a third of the cases. It is distressing that authorities on sterility and urologists maintain a defeatist attitude about a technically difficult but relatively minor surgical attack on a disease with a cure rate of 1:3 or better. A plea is made for more and better anastomoses. O'Connor and Handley have each successfully made scrotal pouches for the storage of sperm in case of block and have each reported successful pregnancy after such technics.

1956 Meetings

In June, at Chicago, the American Society for the Study of Sterility reviewed 22 papers from biochemists, statisticians, internists, surgeons, gynecologists and obstetricians, the subjects varying from "The Role of the Estrogens in Regulating the Metabolism of the Endometrium and the Placenta" to "Factors Influencing Reproductive Potential," including two active panels.

The first of these was on sterility in the female. The second, on sterility in the male, could not substantiate the reported results from the "testosterone rebound" phenomenon. A question from the panel directed to a Chicago co-author of this suggested form of therapy was successfully parried.

Daily for three days there were also ten panels on tests for ovulation, how and where to train physicians to investigate and treat infertility, standards of male infertility, the cervix, psychogenic infertility, treatment and surgery of male infertility, visual methods of diagnosing infertility, artificial insemination, endo-

crine aspect of infertility, failure of endometrium, anovulatory problems and surgery in female infertility.

Unquestionably, the highlight of the three-day conference was the Ayerst Prize Lecture by the eminent Swiss gynecologist Hubert de Watteville, of Geneva, president of the International Association of Obstetrics and Gynecology. In clear, concise, excellent English, this distinguished foreign visitor related that there are undoubtedly psychosomatic influences at work in human beings plagued by infertility, habitual abortion, and stillbirth, but that, in essence, everyone is subject to psychosomatic influences. He did much to scotch the plethora of undocumented psychiatric papers currently crowding the clinical data from the pages of journals devoted to problems of reproduction. His paper should be read by all professional personnel dealing with such problems. Those in the allied fields of adoption, religion, planned parenthood and demography will also profit from his sage analysis not only of the vagaries of patients but also of persons advising, diagnosing and treating human barrenness.

At the hundred and fifth Annual Meeting of the American Medical Association there were excellent panels on disorders of the anterior pituitary body and sexual aberrations in the female. It is anticipated that these papers will be published in coming issues of the *Journal of the American Medical Association*. There was one discussion of cryptorchidism recommending operation by the fifth year of life. This is in direct contrast to the studies of Heller, Snyder, Gross and MacCollum, who believe that just before or at the onset of puberty is the optimum time for treatment. Since irreparable damage to the circulation and spermatogenic function of these delicate gonads may be the result of too early or injudicious surgery, this subject should be critically reviewed and analyzed by general surgeons and urologists co-operating with the less eager of the endocrinologists and pediatricians who are familiar with the recent studies of Charny and Meranze, Sniffen, Howard and Simmons and Lynch. Their histologic studies of preadolescent, adolescent and adult testes imply that the spermatogenic function is, in fact, quiescent until the onset of puberty. Many of these testes will descend spontaneously at or before puberty.

The Hormonal Factor

The hormonal factor in most cases refers to some disorder of ovarian function. Failure of normal function of the ovary is reported in 10 or 15 per cent of infertile couples and may consist of anything from total and complete amenorrhea to deficiencies of the corpus-luteum phase of the menstrual cycle, demonstrated by endometrial biopsy and faulty basal-temperature curves, as well as in some cases by determinations of pregnanediol excretion. This disorder is best recognized by attention to the habitus of the patient, a study of the basal-body-temperature curves and the finding of enlargement of one or both ovaries. Measures that help one make this diagnosis need not be included here, but reference to the work of Tompkins and A. Palmer on temperature changes will offer suitable means of determining this. Buxton, Siegler and others have questioned the value of basal-body-temperature curve, but there is general opinion that it helps to select the approximate time of ovulation and also to determine patients who are not ovulating properly. To assay the functional status of the ovaries more completely Stein has repeatedly emphasized the value of gynecography in his many writings on this score in several countries. More recently Decker, R. Palmer, Cohen, Doyle and Green have demonstrated that direct observation of the ovary by means of the culdoscopy or colotomy may be of value. Decker's recent monograph describes in detail the way to select cases and the technic for doing the procedure and summarizes the interpretation of such tests.

Decker's contribution and the modification introduced by Doyle have certainly increased knowledge of the physiology, function and efficiency of the ovary as well as its diseases. The fact remains, however, that abnormalities of the ovaries, particularly enlargement, should still be investigated particularly by laparotomy because of a possibility of tumor, either cancer or benign, as well as the increasingly common Stein–Leventhal abnormality of the ovary. This consists of thickening of the capsule and interference with the normal ovulation. When 60 per cent of infertile women whose disorder is due to this abnormality of the ovary can be helped to achieve a living child, and 88 per cent can have restoration of the normal menses, it seems an appropriate attack on such faulty ovarian function.

I have found 1 case of cancer of the ovary in a thirty-three-year-old nulliparous patient, and Hertig, Samson and others have reported cancer in the polycystic ovary. There is a distinct place for surgery in human infertility in appropriately selected cases and in appropriately trained hands. Tubal surgery is at the low point on the salvage chart, an average of about 20 per cent successful pregnancies having followed a large number of tuboplasties. The relief of bilateral polycystic ovaries offers a salvage rate as high as 60 per cent. When 2 to 6 out of 10 couples complaining of infertility can be rewarded with a normal, viable child through surgical correction of this disorder, one must again beg that the physician who sees the barren couple weigh carefully his advice that there is "nothing to be done" without consulting up-to-date statistical studies of the salvage from definitive conservative and reconstructive surgery in the barren male or female when indicated.

Habitual Abortions, Stillbirths and Premature Births

Achieving conception does not guarantee a normal pregnancy or a normal birth. It is said that 1 out of

10 pregnancies in this country ends in abortion. Others result in stillborn infants or premature births for various reasons. The couples victimized by these repeated accidents are still infertile in the sense that they are not parents. Unfortunately, space does not permit a detailed analysis of these items, except to point out that the current literature contains increasingly detailed studies and an increasing number of articles on the care and handling of the habitual aborter. Hughes, of Syracuse, has a large preconceptional clinic and in co-operation with Lloyd, and Randall, of Buffalo, has evolved a preconceptional treatment that, although relatively new, holds promise that live, normal infants can be born to patients suffering from habitual abortions. Javert, Speert, Eastman, Greenblatt and Hertig have all contributed ideas on the cause and treatment of abortion. Joel and others have continued to suggest that the male germinal epithelium may contribute to abortion despite MacLeod's emphatic comment that he does not think it is a property of spermatozoa, capable of fertilizing an ovum, to fertilize it abnormally. Since the majority of older physicians and obstetricians are apt to advise patients that there is nothing to be done for habitual abortion, a word of caution here may permit them to send such patients on to a diagnostic clinic or practitioner who is duly accepting the challenge that living children can be obtained for these patients in a higher percentage than was thought possible. The subject of pregnancy wastage has been studied in great detail by Edith Potter, of Chicago, Ayerst Prize Lecturer for 1954, at the meeting of the American Society for the Study of Sterility in Atlantic City. Her publications are definitely required reading for those interested in pregnancy wastage. Ingalls has presented observations of ten years of systematic study of differing insults to pregnant animals that can induce congenital anomalies of the young. He believes that the critical stresses of the mother during pregnancy may determine abnormal growth of the conceptus. The Rh factor, German measles and anesthesia during pregnancy have also been the subject of investigation.

Professor Emeritus H. C. Hesseltine, of the University of Chicago, states: "Most of the pregnancies terminated by abortion were the results of abnormalities which appeared to follow a poor-quality ovum or spermatozoa. Improvement of either the spermatozoa or egg enhances fertility." In an intriguing article in the field of experimental nutrition, "Fat As a Required Nutrient of the Diet," Duel has shown that a single small dose of an unsaturated fat (100 mg. of ethyl linoleate) given three weeks before the animals were bred ensured a normal pregnancy. Since the average wife is engaged in a constant battle to keep her weight at its wedding-day level and shirks fat or consumes only synthetic fat, this isolated statement may be applied to human abortion.

Adoption

Adoption does not correctly enter a discussion of problems of infertility, except for the common supposition that many couples will achieve a normal pregnancy after adoption. The theory has been expressed that this causes a relief of nervous tension, marital tension and possibly psychosomatic changes that allow a previously infertile couple to have a child of its own. No less an authority than John Rock and his co-worker, Hansen, found only 8 per cent pregnancies in a survey of 202 adoptive couples. Then, in his usual terse manner, Rock stated that the literature on the therapeutic effect of adoption on infertility is speculative and without proof, and that Hansen and he do not believe that the 8 per cent of cases presented prove that adoption is a likely cure for sterility. Certainly few of the well studied and well treated infertile couples who failed to conceive before will have children of their own after adoption. There is no doubt considerable basis to the opinion that adoption promotes fertility because impatient couples after two or more years of childlessness hasten to the adoption agency rather than to a modern diagnostic and therapeutic infertility specialist.

Artificial Insemination (Therapeutic Insemination, Semiadoption)

Kleegman and Cary, both supporters of donor insemination, rightly propose that the popular term artificial insemination be replaced by therapeutic insemination, which is what it really is, or semiadoption, which is also what it really is. One partner of the marriage is definitely the parent, and the second partner has in every sense of the word "adopted the child" produced by this treatment. The *Oxford Universal Dictionary* (1955 edition) defines the word adopt as follows: "To take voluntarily into any relationship; especially that of a son." The *Funk and Wagnalls* dictionary (1937) defined adoption as follows:

> To take a child of another as one's own child. Legally, adoption is defined as the act whereby an adult person takes a minor into the relationship of a child and thereby acquires the rights and incurs the responsibility of a parent in respect to such a minor. Ethnologically it is defined as the receiving into the clan or tribe of one from outside, and treating him as one of the same blood.

It is encouraging that such a weighty body as the American Society for the Study of Sterility, according to M. Edward Davis, editor of *Fertility and Sterility,* is the first medical organization without religious affiliation to place itself on record concerning donor insemination. At the June, 1955, annual meeting of the Society a lengthy recommendation was offered on the floor and after free discussion adopted by the members: "If it is in harmony with the beliefs of the couple and doctor, donor insemination is a completely ethical, moral and desirable form of medical therapy." Commenting editorially in March, 1956, Davis goes on to say, "Our voice of approval should echo through the courts of law, the temples of religion, and the halls of science." Reserved for cases in which the wife is within normal limits of fertility and the husband irrevocably sterile in selected couples and

in selected hands, when recommended by a physician and a clergyman who knows the couple well, therapeutic insemination is highly successful. In properly studied and treated cases the possibility of normal pregnancy is 65 to 80 per cent. The success of treatment is best attested by the fact that almost all couples return to have a second child promptly. There are reported cases of as many as 4 children by this cautious therapy. Like all therapy it can be abused and misinterpreted, but in proper hands and properly selected cases those who use it find it mentally, morally, physically and spiritually acceptable. In cases of Rh incompatibility in which a particular husband and wife cannot have a living child of their own it is particularly appreciated. Some victims of war injury and males made sterile by bilateral mumps orchitis or tuberculosis of the epididymis, or congenital absence of the vas deferens, are particularly suitable candidates for this type of treatment when their religion permits it. Patients with cryptorchid testes have no hope of having children otherwise.

The Surgery of Infertility

In well studied cases there is an increasing indication for corrective surgery in male and female infertility. Obstructive epididymitis is relieved by well trained surgeons in 25 to 60 per cent of cases. Repair of varicocele is rewarding in an increasing number of patients. Suspension of the uterus in females having two years of infertility and an adherent third-degree retroversion operated upon surgically by Tompkins has resulted in 75 per cent normal pregnancies in hitherto sterile women. For years Rubin has endorsed myomectomy as a solution to childlessness resulting from fibroids in the uterus, after all other causes of infertility are ruled out. A dozen or more surgeons have reported 60 per cent pregnancies after surgical relief of bilateral polycystic ovaries. Endometriosis, a stigma of the infertile state in many childless marriages, responds to conservative treatment in skilled hands with 30 to 42 per cent pregnancies in operated patients. This is frequently supplemented by the administration of *small* doses of testosterone to hold the endometriosis in check after operation for a few months. Simmons reports that 9 pregnancies followed sublingual administration of testosterone to females with proved endometriosis, and Creadick is quoted as having success in over 30 per cent of his selected cases. Correction of congenital anomalies is successful in the hands of Howard Jones, of Baltimore, and Walter Jones, of Providence, reports 256 pregnancies in 108 cases of congenital anomalies with an abortion rate no higher than 37.1 per cent, and with 65 to 88.2 per cent progressing for thirty-eight weeks. This indicates that even with multiple anomalies pregnancy may still have a successful outcome.

Culdoscopy

Culdoscopy is a surgical maneuver that is primarily a diagnostic tool. It is too early to endorse its free use in infertile females, but it has a high percentage of diagnostic accuracy and has helped avoid surgery for assumed ectopic pregnancies and adnexal masses.

Other Measures

There are reports in the literature of the application of x-rays to the pituitary glands and ovaries of infertile women. In fact there are one or two references to the application of x-rays to the male gonad! There is no doubt that the carefully selected patients of Rakoff and Mazer and Israel, as well as Rubin's contribution to the subject, indicate that faulty ovarian function will be corrected in some cases and that pregnancy with normal children will result. One must not overlook the constant warning of geneticists, such as Muller and Walker, that the x-ray is a destructive force and affects human genes. Since 25 per cent or more of patients approaching infertility clinics conceive ultimately without any conclusive indication of what treatment resulted in this favorable outcome, deliberate exposure of the gonads to the destructive gamma ray seems a hazardous form of treatment. Bishop states that by far the greatest single factor in patients who achieved pregnancy in his clinic was "walking down the ramp" at the Chelsea Hospital in London.

Since cortisone and its allied hormones are being used extensively in all fields of medicine it is inevitable that they should have been reported to benefit ovarian failure. At present it is not possible to condemn or defend their use in disease of the ovary. Certainly, before using them, one should consult the opinions expressed by Seeger Jones in her excellent monograph, *Menstrual Disorders in Sterility,* and the published work of R. B. Greenblatt. Thorn and Sturgis are reopening the question of virilization and the relation between the adrenal gland and the ovary in well controlled studies at the Peter Bent Brigham Hospital. There is little evidence that the administration of cyclic estrogen-progesterone therapy, or the once popular equine gonadotrophic hormone followed by chorionic gonadotrophic hormone introduced by Hamblen et al., is today applicable except to a very few patients. Again, the element of psychotherapy presents itself. The statement of Heller in June, 1956, mentioned above seems apt here: "There is very little place for the use of hormones in the subject of human infertility."

One cannot leave disorders of the ovaries without discussing endometriosis to warn the infrequent operator that what appear like gross abnormalities of the ovary do not require oöphorectomy, either bilateral or unilateral. The incidence of endometriosis is probably about 30 per cent in females, and this disorder is particularly rife in the infertile population. I have seen young women deprived of their gonads by well meaning surgeons who did not recog-

nize that this disease could be resected from the ovary, with functioning ovarian tissue left behind. These endocrine glands, which are essential for reproduction, have other functions and should be handled carefully. The ovary should be preserved, nurtured and encouraged and not mutilated by radiation, the scalpel or bombardment with a display of hormonal missiles.

Likewise, the male gonad, accessible as it is, must not be irritated or depressed by hormone therapy, and certainly not irradiated. Yet it should be placed in its normal environment, early in one's chronologic age, if there is incomplete descent, excessive heat, proximity to a large varicocele, obesity or environmental heat. On the other hand its accessibility makes operative correction a very simple maneuver in men suffering from disorders of spermatogenesis. Testicular biopsy is a means of determining accurately the reproductive capacity of the germinal epithelium, and, again, in skilled hands only, much can be learned promptly about the prognostic future of infertile couples with multiple disorders of infertility in addition to sluggish, reluctant or depleted spermatozoa; biopsy is innocuous and does not destroy gonadal function except in cattle.

Space does not permit a review of the multiple aspects of the administration of thyroid in the infertile population. Since no one has proved that it does harm to euthyroid or hypothyroid persons the majority of workers, although empirically, reiterate that it is useful in infertile couples. The cautious administration of as much as 0.2 gm. (3 grains) a day will continue to solve the problem for some barren marriages. On the other hand, one must be sure to omit or cancel medication to avoid having couples continuing on unnecessarily for longer than a twelve-month period.

If it is assumed that the administration of hormones is generally of little value in the infertile couple and that psychotherapy and possibly psychosomatics enter into the problems of infertility, is it not expedient to remind the reader that complete diagnostic study should be carried out upon both partners of the infertile marriage before it results in indiscriminate and potentially harmful hormonal therapy?

Discussion

Prodded by the complaint of the barren couple and stimulated by the pioneer work of Samuel Meaker, whose *Human Fertility* (1933) is still the master textbook on the subject, I have attempted to promote certain basic concepts of the handling of the sterile couple. Vose, Lawrence, Belding and Rock have given impetus to the search for knowledge of the causes and correction of human infertility. Twenty members of the Greater Boston medical community belong to the American Society for the Study of Sterility, which in the last ten years has grown to a membership of over 500. This group cosponsored the first World Congress on Fertility and Sterility in May, 1953, which attracted over 1200 physicians from 51 different countries to a week-long meeting that resulted in a two-volume set of proceedings of 1528 pages. This enthusiastic response stimulated the second World Congress in Naples, Italy, in May, 1956, attracting 1800 medical scientists from 63 nations, including the Soviet Union. The program left out nothing, was translated into five languages simultaneously, and reminds one of the old bridal custom: "Something old, something new, something borrowed, something blue." The something old was a report that x-ray stimulation of the pituitary gland and ovaries promotes ovulation without causing damage to the genetic characteristics of the patient or her offspring. (This is still a highly controversial subject.) The something new included the series of reports showing that cortisone can "open" closed fallopian tubes without the need for surgery. (This needs considerable confirmation, for it is not sufficient to open the tubes of an infertile couple; a viable offspring is the goal.) Something borrowed included a multilingual discussion of artificial insemination, in which anonymous viable sperm are "borrowed" for the production of 60 to 85 per cent of normal viable offspring. Something blue referred to the technic of administration of methylene blue through the uterine canal and watching it drip out of the fallopian tubes via culdoscopy as indication of patency of the tubes.

According to the *Encyclopaedia Britannica* yearbook there were 66 known infertility clinics in the United States in 1952, and 119 known infertility clinics in 1955, an increase of 53 in three years. Thirty-one of these were under the auspices of planned-parenthood groups, and in addition there were 65 referral centers.

These figures suggest that the medical profession is doing its best to keep up with the demands of infertile couples for relief of their chief complaint, barrenness. It is hoped that the yearly activity in the research laboratories of the basic sciences, veterinary medicine and hospitals will continue to throw out new ideas to be tested by the clinicians. It is also my hope that this review may encourage or persuade not only the first doctor to see the patient but also those professing to study and treat infertility to follow the simple preachings of Meaker, Rubin, Rock, Williams, MacLeod and Miller, of Scotland. These scientists have regularly and repeatedly emphasized the importance of the simultaneous study of husband and wife. In discussing Miller's paper Dr. George W. Corner, director of the Carnegie Institute in Baltimore, said: "Without, in my experience, ever having had to deal with the problem of male infertility, without having undertaken myself studies on testes dysfunction, I can simply say that every point of logic that I have learned, or any other scientific

worker learns in the laboratory, would incline one to support his argument, confirm his argument, merely from the theoretical, if not from the practical standpoint." In other words even the laboratory worker knows that both partners need to be studied. The important problem is how to get this idea across not so much to the patients, who avidly buy anything published on sterility, but to the physicians, who should send the couple on to someone else for study if they are not prepared to do so themselves. Today, there is no branch of medicine from the basic science of anatomy to the profound specialty of psychoanalysis in which something cannot be learned to help those denied a child.

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MEDICAL INTELLIGENCE

HEMORRHAGE FROM DUODENAL ULCER DURING THE ADMINISTRATION OF RESERPINE*

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RESERPINE has become increasingly popular in a wide variety of clinical conditions since its isolation in 1952.[1] The hypotensive and bradycardic action is useful in the treatment of hypertension.[2] The tranquilizing effect is valuable in neuropsychiatric disorders.[3-5] With the larger dosages now being used and the longer clinical experience with reserpine, several serious side effects have been noted. Recent studies have paid particular attention to the gastrointestinal tract.

In dogs, stimulation of gastric hydrochloric acid production by reserpine in both the vagally innervated gastric fistula pouch and the vagally denervated Heidenhain pouch has been demonstrated by Barrett et al.[6] These authors and Barrett, Rutledge and Rogie[7] found that this rise in acid secretion could be inhibited by hexamethonium and oxyphenonium. Schneider and Clark[8,9] showed a significant, sustained hyperchlorhydria after intravenous reserpine in the human subject. This reserpine-induced hyperchlorhydria was not inhibited by atropine, epinephrine or methantheline bromide. The current evidence thus suggests that the action of reserpine on gastric secretion is peripheral[8,9] and possibly on the parasympathetic ganglions[6] or through a humoral mechanism.[8]

Haverback et al.[10] demonstrated a threefold rise in hydrochloric acid concentration with an increase in volume of gastric secretion within sixty minutes of intravenous administration. The response to 2 or 3 mg. daily by mouth was also definitely stimulatory but less strikingly so. The response was noted four to seven days after the drug was begun. These authors described a patient with transient melena and abdominal cramps after reserpine was administered, with prompt disappearance after cessation of the drug. Hollister and his associates[4] reported 2 cases of known asymptomatic ulcer in which symptoms were activated while the patients were taking reserpine.

With the evidence now available it becomes apparent that large dosages of reserpine should probably be used with caution in patients with known or suspected peptic-ulcer disease.[9-10] In the following case of known duodenal ulcer an episode of gastrointestinal hemorrhage developed shortly after oral reserpine therapy was begun.

CASE REPORT

C.J., a 46-year-old man, was admitted to Gailor Psychiatric Hospital on September 19, 1955, in an acute schizoaffective type of schizophrenic reaction. He had experienced 6 such episodes since 1932. The last admission to Gailor Hospital had been in March, 1955. The past medical history revealed mid-epigastric burning pain since 1951. The pain had seasonal exacerbations, mostly in the fall of the year, and was always relieved by milk, antacids and anticholinergic drugs. In February, 1955, an upper gastrointestinal x-ray film revealed scarring of the duodenal cap, but no ulcer crater was seen. There had been an episode of nausea and vomiting, with questionable hematemesis, 10 months before admission.

The patient was given no ulcer therapy during his stay on the psychiatric service and was placed on a regular diet after admission. No electric or insulin shock was given. On September 26 chlorpromazine was started, 100 mg. 4 times a day. The dosage was gradually increased until October 11, when he was taking 1500 mg. daily. On that day reserpine, 4 mg. a day by mouth, was started.

On the night of October 15 an episode of hiccups readily relieved by aluminum hydroxide gel developed. He had been anorectic for 3 days. Early in the morning of the next day he suddenly became nauseated and vomited 300-400 ml. of bright-red blood with clots. There was no associated pain. He was transferred to the medical service of John Gaston Hospital on the same morning.

Physical examination showed a well developed and well nourished man in no acute distress. No abnormal findings were detected.

The temperature was 99°F., the pulse 106, and the respirations 20. The blood pressure was 100/70.

The hematocrit was 36 vol. per cent 6 hours after the hematemesis and was 23 vol. per cent on the next day. After 1500 ml. of blood had been administered the hematocrit rose to 30 vol. per cent and remained stable. The urinary uropepsin was 6480 units per 24 hours. Other laboratory studies were within normal limits.

There was no recurrent hematemesis, though melena was detected. The reserpine and chlorpromazine were discontinued. Frequent milk and cream feedings were instituted, with Pro-Banthine and Amytal Sodium administration. On October 20 an upper gastrointestinal series revealed a constant scarring of the duodenal cap, with a questionable ulcer crater.

Because of the patient's age and mental status, surgical intervention was considered advisable. On October 26 a subtotal gastrectomy with a posterior Hofmeister anastomosis was performed, revealing a duodenal ulcer that had penetrated into the pancreas. The ulcer was not removed. No other probable source of bleeding was encountered in the gastrointestinal tract.

The pathological specimen consisted of 70 per cent of the stomach and a portion of the duodenum. Microscopical examination showed chronic duodenitis with extensive fibrosis.

The patient had an uneventful postoperative course and was discharged on the 10th postoperative day.

DISCUSSION

Parenteral and oral administration of reserpine has been demonstrated in animals and man to pro-

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duce increased gastric secretory activity. Theoretically, this suggests that the alkaloid should be used with caution in the treatment of patients with peptic-ulcer disease. The necessity for caution is confirmed clinically by the observation that reserpine has, at times, been associated with exacerbation of ulcer symptoms and precipitation of gastrointestinal hemorrhage.

In the case presented above, ulcer bleeding occurred five days after the beginning of relatively large oral doses of reserpine. This coincides with the demonstration by Haverback et al.[10] that gastric secretion is increased within four to seven days of the oral administration of reserpine. It is obviously impossible to prove whether drug action here was etiologically or coincidentally related to the ulcer hemorrhage. However, it is believed that a report of this case is justified to emphasize the contention that reserpine may be potentially harmful in the patient with ulcer.

When reserpine therapy is contemplated for a patient with a history of peptic-ulcer disease, attention to proper acid neutralization with diet and antacids appears to be indicated. Since anticholinergic drugs do not seem to counteract the gastric hypersecretion in human subjects, reliance on them alone for protection appears inadequate. In view of the fact that chlorpromazine apparently causes some reduction in gastric secretion (in the subject not receiving reserpine)[10] it may be the agent of choice in the management of neuropsychiatric disturbances in the patient with ulcer that are amenable to tranquilizing-drug therapy.

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CASE RECORDS
OF THE
MASSACHUSETTS GENERAL HOSPITAL

Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

BENJAMIN CASTLEMAN, M.D., *Editor*

VIRGINIA W. TOWNE, *Assistant Editor*

CASE 42511

PRESENTATION OF CASE

A sixty-one-year-old saleswoman entered the hospital because of pain in the back.

Eight days previously she noted the onset of anorexia, nausea and an aching pain in the lower portion of the back that radiated to the inguinal regions. There was one episode of vomiting. Physical examination at that time revealed a soft, nontender abdomen with normal peristalsis. The movements of the back were normal. The temperature was 99.6°F. The symptoms, especially the backache, persisted, but she continued to work every day. On the day of admission the symptoms were worse, and she retched and vomited. Physical examination was negative. There was no accentuation of the pain upon motion of the legs or back. A Kernig sign was not elicited. The temperature was normal.

Three and a half years previously a radical mastectomy was performed for an adenocarcinoma of the left breast, with metastases to 2 out of 10 axillary lymph nodes. One year before admission she was hospitalized elsewhere because of erysipelas of the left arm. Five months before entry a "kink" in the back that persisted for two weeks was noted after she lifted a heavy object. X-ray films of the spine showed slight wedging of the first lumbar vertebra. The pain subsided without therapy.

Physical examination showed a well nourished woman in marked distress because of pain in the lower portion of the back. There was no jaundice, lymphadenopathy or tenderness of the spine. The radical-mastectomy scar on the left was well healed and without evidence of recurrent tumor. Examination of the lungs was negative. The heart was not enlarged. A Grade 2, apical, systolic murmur that was transmitted over the precordium was audible. The abdomen was soft and nontender. Prominent aortic pulsations were felt in the mid-line between the xiphoid process and the umbilicus. The liver and spleen were not palpable. The peripheral pulses were normal. There was no edema.

The temperature was 98.6°F., the pulse 72, and the respirations 24. The blood pressure was 226 systolic, 112 diastolic.

The urine gave a ++ test for albumin; the sedi-

ment contained 3 or 4 red cells, 1 white cell, 1 hyaline and finely granular cast and a few bacteria per high-power field. Examination of the blood revealed a hemoglobin of 12 gm. per 100 ml. and a white-cell count of 16,500, with 85 per cent neutrophils. X-ray films of the chest demonstrated cardiac enlargement, with prominence along the left ventricular contour; calcified scars were seen in both upper-lung fields; the pulmonary vessels were slightly engorged. Films of the lumbar spine showed osteoporosis and minimal wedging of the body of the first lumbar vertebra; there was no evidence of metastatic carcinoma. A film of the abdomen demonstrated a small calcification that lay lateral to the transverse process of the third lumbar vertebra on the left; the left kidney could not be defined; the right was normal; the right lobe of the liver lay rather low; there was a collection of gas in the splenic flexure of the colon, and scattered traces of gas were present in the colon distally, as well as in the small intestine; the psoas shadows were normal; no aortic calcification was visible.

Seventeen hours after admission the patient was noted to be cyanotic and unresponsive. She died a few minutes later.

Differential Diagnosis

Dr. Alfred Kranes*: The problem is to explain back pain, gradually increasing over an eight-day period, accompanied by nausea and vomiting, in a woman who died very shortly after admission. The exact location of the pain is not specified in the protocol; perhaps it could not be localized. The physical examination of the back and the abdomen did not add much, and there is no mention of a pelvic examination but I suspect that that would have added nothing either. Furthermore, there were no helpful laboratory findings aside from a moderate leukocytosis and a few slight abnormalities of the urine, whose significance it is difficult to assess. She did not live long enough for additional examinations of the urine to be done, so we have no further information about the state of the kidneys.

May I look at the x-ray films?

Dr. William Brown: The films of the lumbosacral spine taken five months before admission show normal kidney outlines on both sides, normal psoas shadows and the caudate lobe of the liver extending downward but not indicating a hepatic enlargement. The spleen is within normal limits, and the bone is basically normal except for the fact that there is a minimal wedging of the first lumbar vertebra. The character of the bone is normal; there does not seem to be any evidence of metastases to the bones. This wedging is on the basis of old injury or compression of the spine by weight. The films of the chest taken on admission demonstrate prominence of the left ventricle, elongation of the cardiac silhouette and tortuosity of the aorta, the last two being consistent with the age of sixty-one. There are some scattered calcifications in the upper-lung fields as persistent evidence of old, healed granuloma, none of which are active. The diaphragm is normal. In the films of the abdomen the right kidney is clearly outlined; the left kidney is not so well seen at this time as in the previous examination. There is a calcific density to the left of the transverse process of the third lumbar vertebra; this is constant on two films and could represent ureteral calculus.

Dr. Kranes: Could that be aortic calcification?

Dr. Brown: I think that is the vertebral transverse process. There has been no change in the lumbar spine, and the character of the bone is not abnormal.

Dr. Kranes: Is that an unusual place for a phlebolith?

Dr. Brown: Yes; I should not expect a phlebolith to be in this area. There is no visible calcification of the aorta, on either the anteroposterior or the lateral films. The accumulation of gas mentioned in the protocol is in the splenic flexure of the bowel; it is remarkably constant and raises the question of an isolated loop of large bowel or of an abscess, particularly in view of the fact that the kidney is not well seen.

Dr. Kranes: Habitually, for some years, when receiving a protocol for discussion at a clinicopathological conference, after reading the first sentence I turn to the last sentence, where it states that the patient was either operated on or died, generally giving the circumstances under which the patient died. On the basis of that rather meager information I make a list of the various diagnostic possibilities. Then, as the story unfolds, some of these become either excluded or rendered less likely, and often additional diseases present themselves for consideration. This sixty-one-year-old saleswoman entered the hospital because of pain in the back and died rather suddenly, although the exact details were not given, seventeen hours after admission. Had she been watched carefully, Dr. Kelley?

Dr. Rita M. Kelley: She had received a hypodermic injection of Demerol for pain at about 2 p.m., with relief of pain, and then she did not require another injection until 1 o'clock the next morning. After each injection she went to sleep. At six or seven o'clock in the morning she put on her light; when the nurse went to see her she was cyanotic and comatose and died shortly thereafter.

Dr. Kranes: There was a period, then, of some hours during which she may not have been seen; therefore, she may have been moribund longer than seems apparent from the record.

When I tried to make a list of diseases that produce pain in the back and nausea, as well as sudden death, I found myself in the embarrassing position of being able to think of only a few diseases. As I read the remainder of the protocol, I was unable to suggest anything else worth discussing. I then began to wonder whether the pain in the back was related to the

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manner of death. Perhaps the patient died of an unrelated cause. She may have had any one of a dozen diseases that are capable of producing pain in the back, and she may have died of any one of several acute pulmonary or cardiac disturbances. She may, for example, have had metastatic carcinoma of the spine, in spite of the fact that the x-ray films did not reveal it, and she may have died of myocardial infarction. Or she may have had a carcinoma of the tail or body of the pancreas, which so often leads to deep venous thrombosis, and she may have died of a pulmonary embolus. These and many other combinations are possible; I see no way of excluding them because there is no information on which to rule them in or out. However, it seems to me that if the pain in the back and the sudden death had no relation to each other, this becomes a guessing game, rather than a teaching exercise — a contest between the clinician and the pathologist (a very unequal contest, since the pathologist holds all the high cards). For this to make any sense, I have to assume that the backache and sudden death were related; therefore, I am back where I started, with only two diseases that I know can explain both the backache and the sudden death, and one of them is not very plausible.

The first is that the patient suffered from renal disease, which resulted in hypertension, and that death occurred as a result of an attack of acute pulmonary edema. The evidence for acute renal involvement, of course, is not strong. There was only one examination of the urine, which showed a little albumin, several red cells and occasional casts. Whether these represented evidence of renal disease or whether they represented what Osler referred to when he wrote on the advantages of a little albumin and a few red cells in the urine I do not know, but these findings alone are not enough to make a diagnosis of renal disease. Furthermore, the only type of renal disease that would be capable of producing this much pain in the back is a stone. Unfortunately, there is a shadow in the x-ray films that might be a stone. If there was a stone in one kidney only, it would have been unlikely to produce hypertension of that degree and lead to pulmonary edema. The process would have had to be bilateral, rather than unilateral; so that, not unwillingly, I gave up this diagnosis.

The only other possibility that made sense to me was a rupture of the abdominal aorta — a rupture either of an aneurysm or of a dissection. If it was an abdominal aneurysm, I can reconstruct the picture by assuming that eight days before admission the aneurysm first began to leak and produced pain in the back; as the leakage increased, symptoms increased. The obscuration of the left kidney noted in the x-ray films may indicate that the retroperitoneal area had been infiltrated with blood. As you know, there is often a considerable delay — sometimes a matter of weeks — between the initial bleeding from an abdominal aneurysm and the terminal massive hemorrhage. That is fortunate because it may give the surgeon ample opportunity to operate, when the diagnosis can be made. It is also fortunate that the majority of such aneurysms are below the level of the renal artery, so that they can be removed and aortic grafts put in. There may be more than one aneurysm, including not only the aorta but also the iliac vessels.

There is a statement that prominent aortic pulsations were felt between the umbilicus and the xiphoid process. How much importance to attach to that is difficult to know from the printed page. One would like to feel the pulsation oneself to evaluate it. In a stocky person it is not common to feel prominent aortic pulsations in the upper abdomen. Since this patient was described as well nourished this observation may be of some importance and suggests the possibility of an aortic aneurysm.

While I am on the subject of abdominal palpation, I should mention the fact that many patients with abdominal aneurysms have a habit of dying within twenty-four hours of admission, particularly to a teaching hospital. I have often wondered whether that may be the result of the exceptionally careful examinations they undergo, first by the student and later by the assistant resident, the resident, the visiting physician, the consultants and so on. In these patients such multiple examinations are a distinct hazard that should be borne in mind.

Only one feature bothers me in this diagnosis — that is, the terminal cyanosis. I should expect a ruptured abdominal aneurysm not to produce cyanosis, but pallor. This makes me wonder about the possibility of an aortic dissection. The final adventitial rupture of a dissecting aneurysm is likely to be either into the pericardium or into the left pleural cavity, both of which may result in cyanosis. However, other aspects of the story make a dissection somewhat unlikely. In most cases of aortic dissection there is likely to be much more pain in the anterior portion of the chest or in the abdomen. The pain is not likely to be localized to the back for such a long time. Most dissections, the overwhelming majority, begin in the thoracic aorta. Rarely, the abdominal aorta may be the site of a large intimal tear, but it is the dissection that produces the pain.

It is a little difficult to choose between the two possibilities, but in spite of the cyanosis I favor a ruptured aneurysm of the abdominal aorta.

DR. ARTHUR S. PIER, JR.: Would you not expect a palpable mass in the abdomen and also some abdominal pain with an abdominal aneurysm?

DR. KRANES: Not necessarily. The presence of a mass would depend entirely on the size of the aneurysm, whether it was fusiform or saccular and whether it presented anteriorly or laterally as so many of them do. The pain I should interpret as produced by leakage of blood into the retroperitoneal area; if no blood got into the peritoneal cavity, I do not think tenderness would necessarily occur.

DR. LEWIS W. KANE: Would you not expect that an abdominal aneurysm would be visible in the x-ray films?

DR. KRANES: Yes; I should. Many of these have

calcification in the wall, but the absence of calcification does not rule it out.

DR. JACOB LERMAN: Would you commit yourself on a metastatic tumor?

DR. KRANES: As I said, that would be a pure guess. I did not commit myself.

DR. ROGER A. MELICK: A subarachnoid hemorrhage might present with pain in the lower back, produced by leaking down of blood. The patient may have had a leaking intracranial aneurysm.

DR. KRANES: That is one possibility that did not occur to me.

DR. BENJAMIN CASTLEMAN: Did she have any headache?

DR. KRANES: An aneurysm of the vertebral artery may produce subarachnoid hemorrhage and backache. One of our prominent physicians died in that manner.

DR. WINFIELD S. MORGAN: Dr. Kelley, have you a comment?

DR. KELLEY: I should like to add a little background. This woman was a head saleswoman in the children's book department of a large store. I saw her on New Year's Day after she had lived through the Christmas rush. On that day the emphasis was on the gastrointestinal tract, rather than on the pain in the back. The back pain was incidental. I treated her symptomatically and told her to stay home from work for a couple of days and let me know if she felt no better. This was just at the height of a viral epidemic last year. I heard no more from her except from another patient, a friend of hers, who said that she had gone to work and would not stay home. The next time I saw her was five days later, when she had the severe back pain, nausea and vomiting. I immediately sent her into the hospital.

We thought of metastatic disease and also of a dissecting aneurysm or possibly a rupture of an aneurysm, but in the presence of normal peripheral pulses, normal psoas shadows and rapid relief from Demerol we decided to watch her until the next day, but there was no next day.

DR. KRANES: How prominent were the abdominal pulsations?

DR. KELLEY: They were not any more prominent than those that many hypertensive patients show.

This woman had had hypertension for as long as I had been following her. She had come to me originally because of urinary frequency. The carcinoma of the breast was picked up as a purely incidental finding. When she came into the hospital for that operation she had several renal-function tests; they were all negative except for occasional + or ++ tests for albumin.

DR. KRANES: I should like to comment on what Dr. Kelley said about the gastrointestinal symptoms, which I meant to do during the discussion. This interested me very much and reminded me of a patient with an abdominal aneurysm whose primary symptoms were nausea, vomiting, abdominal distention and bloating. About eight years ago Ogilvie* described cases in which invasion of the retroperitoneal area, usually by tumor, was associated with an actual intestinal obstruction. It has become known, in the British literature at any rate, as Ogilvie's syndrome although I have not seen it thus referred to in the American literature. Infiltration of the retroperitoneal area with tumor or blood may cause gastrointestinal symptoms, suggesting obstruction.

CLINICAL DIAGNOSIS

?Dissecting aneurysm of aorta.
?Myocardial infarction.

DR. ALFRED KRANES'S DIAGNOSIS

Ruptured aneurysm of abdominal aorta.

ANATOMICAL DIAGNOSES

Ruptured mycotic aneurysm of abdominal aorta.
Retroperitoneal hemorrhage.

PATHOLOGICAL DISCUSSION

DR. MORGAN: The pathological findings were in the abdomen. The most remarkable aspect of this case is the fact that the patient did not have more symptoms before entry to the hospital. When the abdomen was opened, about 1.5 liters of blood was found in the retroperitoneal area on the right side, surrounding the right adrenal gland and kidney and extending down from the leaf of the diaphragm to the crest of the ilium and into the pelvis. On the anterior aspect of the aorta, adjacent to the origin of the inferior mesenteric artery, was a defect in the wall, with rounded edges, measuring about 2 cm. in greatest dimension. There was only slight atherosclerosis in the aorta. This hole in the wall communicated with a cavity anteriorly and somewhat to the left, which contained about 100 ml. of blood. Recent expansion of this cavity may well explain the obscuring of the left-kidney outline seen in the x-ray films. The anterior wall of the cavity was formed by very dense, tough connective tissue, and at our gross conference the interpretation was that this tissue actually consisted of metastatic tumor that had infiltrated the aorta and produced this unusual appearance of the wall. Our microscopical sections, however, revealed that this was acute and chronic inflammatory tissue, with many colonies of bacteria scattered throughout it. There was a great deal of scarring in addition.

I think we can reconstruct the case in this way: sometime in the past — and I cannot tell when from the protocol — an abscess developed in the aorta. I am afraid we also do not know its source. The inflammation smoldered along over an unknown period, probably months in view of the degree of scarring in the area, and finally eroded and weakened the wall, causing the defect previously described. The constant pressure of the blood led to outpouching of the ad-

*Ogilvie, H. Large-intestine colic due to sympathetic deprivation: new clinical syndrome. *Brit. M. J.* 2:671-673, 1948.

ventitial tissues of the area and the formation of a pseudoaneurysm. The bacterial growth persisted and extended, finally weakening the wall of the pseudoaneurysm and leading to terminal rupture.

DR. CASTLEMAN: Dr. Kelley, do you recall whether the patient had any previous infection?

DR. KELLEY: The only infection was the erysipelas a year before admission. I did not see her at that time; she went to another hospital. I had not seen her for a year and a half before this house call on New Year's Day. She was the kind of person who did not pay much attention to her health unless some real difficulty turned up.

DR. LERMAN: Was the hemorrhage on the right side or the left?

DR. MORGAN: It was on the right side.

DR. LERMAN: The x-ray films seem to show it on the left side.

DR. MORGAN: The terminal rupture was into the right side, but the original tear and slow leakage was on the left.

DR. PIER: Were the heart valves normal?

DR. MORGAN: Yes; they were carefully examined, and there was no evidence of endocarditis.

CASE 42512

PRESENTATION OF CASE

A sixteen-year-old schoolgirl was admitted to the hospital because of pain in the back.

Two weeks previously she noted a persistent aching pain in the region of the dorsal spine that gradually increased in intensity. The pain was not affected by respiration or change in position. It became severe enough during the two days before entry to interfere with sleeping. There was no history of trauma.

Physical examination revealed a well nourished, normally developed girl who complained of pain in the back to the right of the mid-line at the level of the eighth and ninth thoracic vertebras. There was no tenderness in this area or in the spine.

The temperature was 98°F., the pulse 72, and the respirations 16. The blood pressure was 124 systolic, 90 diastolic.

The urine was normal. Examination of the blood revealed a hemoglobin of 13.8 gm. per 100 ml. and a white-cell count of 9700. The total protein was 7.2 gm., the calcium 10.4 mg., and the phosphorus 4.3 mg. per 100 ml. The alkaline phosphatase was 3.5 units. A tuberculin skin test (O.T. 1:1000) was negative. X-ray films of the thoracolumbar spine demonstrated extensive destruction of the body of the eighth thoracic vertebra, involving the right side more than the left, with reduction in size of the vertebral body to less than half its normal height (Fig. 1); the right pedicle was largely destroyed, with probable extension of the destructive lesion to the right transverse process; there was some associated swelling of the soft tissue on either side; the intervertebral spaces were well preserved. Films of the skull, chest and pelvis were normal.

An operation was performed on the second hospital day.

DIFFERENTIAL DIAGNOSIS

DR. PAUL M. G. ST. AUBIN*: Associated with the destruction of the eighth dorsal vertebra described in the protocol is a mild dorsal kyphosis and scoliosis with convexity to the left. The vertebras and intervertebral spaces above and below are intact, and there is minimal bulging of the paravertebral soft tissue not inconsistent with the degree of vertebral collapse. Within the collapsed vertebral body there is an area of bone destruction with sparing of the anterior and left

FIGURE 1. *Anteroposterior View of the Thoracic Spine. There is compression of the body of the eighth thoracic vertebra, which shows increased radiolucency, and thickening of the paravertebral soft tissue opposite the involved vertebra.*

portions of the body and complete destruction of the right pedicle and part of the cancellous bone in the right transverse process. A number of cortical breaks along the superior, inferior and right lateral surfaces are noted; although some of these are no doubt the result of the pathologic fracture, the loss of cortex in the right lateral aspect of the vertebral body must be the result of a primary osteolytic process. There is no evidence of new-bone formation or patchy amorphous calcification. The remainder of the films—those of the chest, the rest of the spine, the pelvis and the skull—show no lesions of the bone or other abnormalities. There is a suggestion of some enlargement of the spleen.

This adolescent girl suddenly had back pain of sufficient constancy and severity to cause her to seek medical attention within two weeks of onset, and had no other symptoms or signs. The lesion on the films is destructive, not sharply defined, and has grown to a size sufficient to weaken the structural rigidity of the

*Assistant radiologist, Massachusetts General Hospital.

eighth dorsal vertebra and permit collapse of a portion of this structure. It can be assumed with moderate certainty from the history and lack of osteophytic reaction about the vertebral body that the collapse occurred recently and probably concomitantly with the onset of pain. Apparently, during the period of its growth it produced no significant symptoms and did not affect the body function sufficiently to alter laboratory tests carried out at the time of admission.

If this were a few decades ago or if we were in some other geographic location, the first consideration in a patient of this age with a collapsed mid-dorsal vertebral body would be tuberculosis. With the degree of bone destruction, however, it would be surprising in tuberculosis not to see involvement of the disk spaces above and below and greater bulging of the paravertebral tissues. The short history, lack of febrile episodes, normal white-cell count, negative tuberculin test and lack of tenderness over the area are against the diagnosis of tuberculosis. Infection generally can be excluded on these same premises.

I suppose such entities as torulosis, blastomycosis and echinococcal disease should be mentioned, but their rareness hardly makes them worth considering. Gumma of bone can occur at this age but this lesion is equally rare today. I am thus excluding infection as a cause of the lesion.

The second general consideration that comes to mind is tumor. Certainly, on first glance this lesion in a person sixteen years of age could represent a malignant process, such as a Ewing sarcoma or lymphoma. Here, a major decision has to be made from the historical and radiographic material available regarding the basic character of the lesion. Is the lesion, if a tumor, malignant or benign? The destruction of the cancellous portion of the vertebral body, the loss of areas of cortical bone and the destruction of the entire right pedicle strongly suggest a malignant process. But it would be remarkable for a malignant tumor to cause so much local destruction of cancellous bone without greater destruction of cortex and spread beyond the bony confines into the surrounding soft tissues, producing related symptoms at an earlier date than were recorded here. Also, the suggestion of expansion of bone in some areas is strongly against malignant tumor. The films in the lateral projection suggest a bulging of the intact cortex posteriorly and superiorly. Nor is there support for a diagnosis of malignant bone lesion from the clinical laboratory data that show a phosphatase within normal range and a hemoglobin that is not remarkable for an adolescent girl. It is true that the patient's spleen appeared larger than normal, but she was racially of Mediterranean origin and these people frequently have larger spleens than northern Europeans do. Some of these arguments may appear weak individually but in total are adequate, I believe, to enable me to discard the diagnosis of primary or metastatic malignant neoplasm of bone.

The lesion, therefore, was benign and, so far as can be determined from the study, was limited to the eighth dorsal vertebra. Of the benign bone neoplasms, giant-cell tumor is certainly a consideration. Since Jaffe et al.[1] question the existence of this lesion in vertebral bodies, and particularly at this tender age, I am in no position to start campaigning for its existence. Apparently, the lesions of the vertebral body tagged as giant-cell tumors have proved to be aneurysmal bone cysts in the majority of cases. In the lateral projection the posterior margin of one of the areas of bone destruction extends to the cortex, and the cortex appears to bulge. Anteriorly and in the right transverse process, however, the margin between the destroyed and intact cancellous bone is ill defined, and there is an irregular fading of one into the other. I believe the radiologic appearance goes not only against aneurysmal bone cyst or giant-cell tumor, if this indeed occurs, but also against a chondroma, which occasionally arises in the vertebra. Chordomas in this location and lipomas of the vertebral body are so rare that I shall automatically exclude them.

A third process, eosinophilic granuloma, is certainly a consideration in this age group, in this location and with a lesion of this radiologic appearance. The normal laboratory data are not against this, although an eosinophilia and slight elevation of temperature might have made the diagnosis easier. Was an eosinophil count done, or was a differential count done on the white cells?

DR. BENJAMIN CASTLEMAN: There were no eosinophils in the blood smear.

DR. ST. AUBIN: I do not think the lack of tenderness on physical examination is against an eosinophilic granuloma, although tenderness is a frequent occurrence. The ill defined, gradual blending of intact cancellous bone with destroyed bone, the limited areas of cortical destruction, some of which were no doubt the result of the compression fracture, and the lack of a gross tumor mass extending beyond the vertebral body from the clinical radiographic evidence more strongly favor an eosinophilic granuloma. I believe that it is perfectly safe in this situation to make a diagnosis of a benign process from the radiologic appearance. With some temerity I limit this to two possibilities — an aneurysmal bone cyst and eosinophilic granuloma; on rather tenuous evidence I have chosen the latter as my diagnosis of this bone lesion.

DR. JACOB LERMAN: Is a hemangioma of the bone the same as an aneurysmal bone cyst?

DR. CASTLEMAN: A hemangioma is a true neoplasm made up of proliferating blood vessels. An aneurysmal bone cyst is composed of large, vascular spaces filled with blood, which probably results from a local circulatory disturbance. It may be related to an arteriovenous anastomosis.

DR. ST. AUBIN: Actually, the radiographic appearance of the lesion under discussion bears no resemblance to a hemangioma of a vertebral body. Although such lesions do occur at this age, they are more frequent in the older generation. They characteristically show a coarsening of the vertical cancellous

bone striations, with enlargement of the vertebral body, and rarely collapse.

DR. MARIAN W. ROPES: I agree with Dr. St. Aubin that infection is less likely than tumor. I find it a little more difficult to be sure that it was a benign rather than a malignant process, such as a lymphoma.

DR. H. L. HEYL: Could an ossifying center ever produce such a picture?

DR. ST. AUBIN: I doubt it very much, although osteochondritis of the primary center of ossification can cause wedging.

A PHYSICIAN: At what age did the menarche occur in this patient?

DR. CASTLEMAN: That was not recorded.

DR. BERNARD M. JACOBSON: Dr. St. Aubin, did you say why you thought this was not myeloma?

DR. ST. AUBIN: I did not mention myeloma, for I believed that the age was very much against it.

DR. CASTLEMAN: I do not believe that we have seen myeloma in anyone that young. Many of the cases of myeloma in children that have been reported have later been shown to be examples of eosinophilic granuloma.

Dr. Fornshell, will you tell us the opinion on the ward?

DR. ROBERT P. FORNSHELL: Our reasoning was about the same as Dr. St. Aubin's. We thought, at first, that the possibility of malignant tumor was greater, but on further study decided it was more probably a benign process. We considered the giant-cell tumor as well as an aneurysmal bone cyst. After discussion with the general surgical service it was thought that better exposure could be obtained through a transthoracic approach. I do not believe that it was mentioned in the protocol that the lesion was biopsied first.

CLINICAL DIAGNOSIS

?Aneurysmal bone cyst.
?Giant-cell tumor.

DR. PAUL M. G. ST. AUBIN'S DIAGNOSIS

Eosinophilic granuloma.

ANATOMICAL DIAGNOSIS

Osteogenic fibroma of vertebra.

PATHOLOGICAL DISCUSSION

DR. CASTLEMAN: A needle biopsy was done, but it revealed no definite tumor that we could see. There were many giant cells and what we thought was the wall of a blood vessel, surrounded by many inflammatory and connective-tissue cells. From the needle biopsy we thought the lesion was consistent with aneurysmal bone cyst. With that preoperative diagnosis the surgeons explored and found pink-gray, granular material that they were able to curette. When an aneurysmal bone cyst is exposed, there is usually a gush of blood. That was not true here, so that at operation the lesion did not appear to be an aneurysmal bone cyst. We did a frozen section on the curetted material and found that most of the lesion was made up of benign connective-tissue cells. In the final sections we saw a number of giant cells, which are in almost any bone lesion that has had some bleeding into it or irritation of some sort, and connective-tissue cells. The striking finding was that the matrix between the connective-tissue cells contained a great deal of osteoid. This tumor, therefore, is what is called an osteogenic fibroma — a benign connective-tissue tumor producing bone. Because of the presence of many giant cells this lesion has often been incorrectly called a giant-cell tumor, and because of the presence of osteoid, it has also been incorrectly called an osteogenic sarcoma. This lesion is commonly found in the vertebra, although there have been some reported in the long bones. Because of the osteoid-producing nature of the lesion, some pathologists have gone so far as to say this is a type of osteoid osteoma — a giant osteoid osteoma.[2] The osteogenic fibroma does not contain the small nidus that is the *sine qua non* of the osteoid osteoma. I personally should prefer to limit the diagnosis of osteoid osteoma to cases with the already accepted criteria clinically, radiographically and pathologically.*

DR. ROPES: It is interesting that the alkaline phosphatase was normal.

DR. CASTLEMAN: The tumor involved only one vertebra.

A PHYSICIAN: Do you see osteoid in fibrous dysplasia?

DR. CASTLEMAN: Yes, but in fibrous dysplasia there is immature bone and cartilage. This tumor did not look like that.

DR. ARTHUR S. PIER, JR.: Does an eosinophilic granuloma form osteoid?

DR. CASTLEMAN: No; it does not. There were no eosinophils or histiocytes in the case under discussion. There was no granulomatous reaction at all.

DR. ROGER A. MELICK: Is this the same as the so-called nonossifying fibroma?

DR. CASTLEMAN: No; the nonossifying fibroma does not have any osteoid; it is just a straight fibroma.

DR. ALLEN G. BRAILEY: What will the lesion do now? Will it fill in with bone?

DR. CASTLEMAN: A piece of ilium was transplanted, and the vertebra fused. I think that it will heal.

DR. FORNSHELL: The material was curetted; there was no reaction around the mass at all, and the body was collapsed. We curetted it out as far posteriorly as we dared.

*Lichtenstein[3] has just proposed the name "benign osteoblastoma" for this tumor, thus making it analogous to the cartilage-forming tumor, benign chondroblastoma.

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The New England Journal of Medicine

Official Organ of
THE MASSACHUSETTS MEDICAL SOCIETY

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AWAY IN A MANGER

A CHRISTIAN day of commemoration, Christmas is nevertheless of such broad significance that it can be respected by all who worship a single God of mercy, regardless of their differences in form of worship and of their various leaderships. This possibility of wide appreciation was indicated recently by a Protestant minister in a sermon on "The Simple Truth," in which he referred to a colleague of a different denomination who had similarly preached on "Being Like Jesus."

The messages were the same, that Christianity, despite its various creeds and the intricacies of worship that have developed in its name, is based on simple, fundamental rules of conduct and of devotion laid down by a simple and direct spiritual leader. As Gandhi once said to a Christian missionary, it is not the spoken word of Christianity that has any wide effectiveness, but the actions of Christians when they seek to emulate the life of Christ. And it is in this emulation, this imitation, conscious or unconscious, that the virtue of Christianity lies. This is something not completely integrated with the parade and pageantry of organized observance as practiced by so many churches and followed by so many "professed" Christians.

Understanding without initial belief is more promising than belief without understanding. All who are willing can attempt this understanding, and a community of tongues and nations and religions will be more nearly approached when more genuine attempts are made by each to comprehend the ideals, the problems and the reasoning of the others.

The directness of the simple truth as exemplified, particularly for Christians, in the life of Jesus is undeniable. This can be generally appreciated, especially at this season, as a cohesive force that might become more powerful than the divisive effects of multiple but relatively unimportant sects and creeds and churches and religions, all trying to find help and guidance from a single Deity despite a diversity of prophets and of interpretations.

For the pomp and circumstance of many of the established customs of worship are far removed from the life, the teachings and the character of Christ. Perhaps once a year is not often enough for the world to be reminded that simple truths can have their origin in a manger.

FOR THE SAKE OF HUMANITY

DESPITE the fact that the passage of a "pound bill" is a vital consideration if Boston is to maintain its pre-eminence as a medical center, the General Court of the Commonwealth of Massachusetts has continually rejected any legislative proposal designed to make stray, unclaimed, unwanted — and doomed — animals in public pounds available for medical research and teaching purposes.

Even in the face of overwhelming evidence of the need for such legislation, of the invaluable contributions to medical progress made through research on animals and of the basic humanity of animal research, the legislators, besieged by the minority that the New England Antivivisection Society represents and harassed by certain elements in the daily press, rejected overwhelmingly all attempts by sincere, dedicated and humane men and organizations to effect passage of a pound law. It is to the credit of these men and organizations that, despite the legislative rebuffs and the vilification they have personally received for the courage of their convictions, they are willing, once again, to seek passage of a pound bill.

Filed this year for consideration by the General Court in 1957 is a bill that, like its predecessors, will make animals from public pounds available for medical research and teaching. The bill has for its sponsors a long, impressive list of medical and allied medical organizations and lay groups.

Animals now used by research and teaching centers in Massachusetts are obtained through dealers. The supply is inadequate, the service undependable, and the cost almost prohibitive, and it is conceivable, under existing arrangements and safeguards, for a pet eventually to find its way into a research center through purchase of a supply from an unscrupulous dealer.

The pound law, as proposed, will eliminate the relation between the institution and the animal dealer, and in its place effect a procedure that will guarantee that only unwanted, stray and unclaimed dogs and cats will be used by research and teaching centers. The bill may well be termed a "pet-saving" law.

The proposed bill would be administered by the Commissioner of Public Health, who, after proper investigation, would issue to various institutions licenses (valid for one year) allowing them to obtain from the pounds animals scheduled for slaughter. The bill provides for adequate inspection of the laboratories.

Over 100,000 dogs and cats are destroyed in Massachusetts pounds each year. On the other hand it is estimated that for the year 1957 the research and teaching centers in Massachusetts will require 5050 dogs and 1400 cats — a small percentage of those slaughtered annually.

Dogs and cats selected by the licensed institutions will unquestionably receive far better treatment in the animal laboratories than they have ever known. Their contribution to medical progress and teaching and to veterinary medicine needs no recounting in these columns.

It is impossible not to believe that the State legislators, now more fully aware of the contributions of animal research and the basic need for pound legislation, will in their wisdom vote the passage of the bill, thus helping to assure Boston's continuance as a world medical center and thus demonstrating their faith in man's humanity to man — and to animals.

THE ROUND TABLE

THOSE who were acquainted with the late Robert Montraville Green, surgeon, obstetrician, associate professor of anatomy at Harvard and one-time editor-in-chief of the *Journal*, knew a rare person indeed. A graduate of Harvard College *summa cum laude* in English and the Classics, a Greek and Latin scholar, he retained throughout his life a devotion to learning in general and especially to letters.

Nor was his interest purely passive, for he was constantly writing and translating; two years ago, as mentioned in these pages at the time, the Club of Odd Volumes published a translation of the odes of Quintus Horatius Flaccus that had been prepared by Dr. Green and the late Dr. Fred B. Lund in collaboration, and in 1955 his translation of Asclepiades made its appearance. There were relatively few persons aside from his friends, however, who knew of Robert Green's real life-long avocation—his *parergon* —the first fruit of which has now been published by Mrs. Green, nearly a year and a half after its author's death. This is *The Round Table — An Arthurian Romance Epic,* printed by the Eliot Press in Jamaica Plain. A book of 20,000 lines — the first of five volumes — it constitutes the base of a truly remarkable literary monument to a distinguished scholar and doctor afield.

While still an undergraduate Dr. Green became interested in retelling "the entire cycle of Arthurian romances, doing for them in verse what Malory did in prose, and restoring to their canon what Malory omitted." For the next ten years, through medical school, hospital services and the starting of a practice he studied sources, immersing himself in the Arthurian tradition before setting at the writing of an epic poem, which, still published only in part, occupied his precious moments of leisure for the remaining forty years of his life.

As the author frankly admits in his preface he no more allowed himself to be restricted by consistency than did Malory or the other Arthurian narrators. For the whole collection of tales is a romantic inconsistency, built up around the legendary hero of a primitive race, yet in the medieval setting of the Age of Chivalry, six centuries later. In defending such an anachronism as the introduction of Salerno and Dame Trot into a narrative of the sixth century, Dr. Green points out that its freedom from conditioning by fact, space or time is the very essence of romance.

In all modesty he quotes the unknown phrase maker who said that "he who nowadays writes a book of verse is like one who throws a rose petal into the Grand Canyon and then listens for the echo." It is not necessarily an echo, however, that one is await-

ing; and regardless of echoes, in what more inspiring setting could one view a rose or even a petal from one?

The narrative is compelling, and its author emerges still more clearly as a physician-scholar whose like is all too seldom seen.

> And passing was their joy, and joyously
> They journeyed on through budding English lanes
> Of hawthorn.

INNOCENCE ABROAD

THE *Journal* takes pleasure in announcing a mutually reciprocal block-booking arrangement that has been entered into with the *Practitioner* of London, whereby bona fide subscribers to each periodical may obtain the other at a reduced rate. The details of the strategy are explained on page xxvi of this issue of the *Journal*.

The *Practitioner*, one of the most highly esteemed of the British medical publications, was founded in 1868; in October, 1951, it celebrated the bringing forth of its thousandth issue, which represents a host of deadlines courageously met and triumphantly overcome. Not a haphazard journal, relying for its scientific pabulum on what the neighbors may bring in, as they say in rural New England, the *Practitioner* plans each issue far ahead, and each comprises a symposium on a subject of interest to the practicing physician, with a number of special features in addition. The *Practitioner* is currently edited by Sir Heneage Ogilvie and Dr. William A. R. Thomson, with a consultant editor in the United States.

Several times a year specially prepared articles by American authors are published, and many distinguished names from this side of the Atlantic have appeared in the list of contributors. The Boston school happens to figure prominently in the issue of October, 1956. This special number on "Advances in Treatment" contains an article on "Advances in Surgery," by Drs. Richard B. Cattell and Bentley P. Colcock, of the Lahey Clinic; a contribution on "Advances in the Treatment of Skin Diseases," by Dr. John G. Downing, professor emeritus of dermatology at Boston University and Tufts University schools of medicine; and one on "Advances in the Treatment of Chronic Rheumatic Diseases," by Dr. Walter Bauer, Jackson Professor of Clinical Medicine, Harvard Medical School, and Dr. Marian W. Ropes, assistant clinical professor in medicine, Harvard Medical School.

It is, of course, not the purpose of the editors of the *Journal* to imply for a moment that the *Practitioner* need supplant the *Journal* in the esteem of its subscribers, but only that the two are unusually well suited for a happily independent symbiotic relation, with science and social consciousness again transcending political considerations.

Besides amputations of limbs, that of the testicles seems to have been successful in curing epilepsy.

Boston M. & S. J. *December 25, 1856*

BOSTON MEDICAL LIBRARY

FROM THE CURATOR'S NOTEBOOK

It was just fifty years ago that Dr. Morton Prince wrote his book, *The Dissociation of a Personality* (New York, 1906). Dr. Merrill Moore, when asked to comment on the golden anniversary of one of the outstanding books of the twentieth century, much of the substance of which was presented at meetings of the Boston Society of Psychiatry and Neurology held in Sprague Hall just after the turn of the century, replied as follows:

> It is well to remember that the publication of this book marked the beginning of what might be called the popular era of dynamic psychology in medical and general literature. The book was an amazing success from the first. Dr. Prince wrote it in a way that would be readable for anyone with a high-school education. With all its simplicity, the book puts forth a profound concept of personality that has been re-examined by later writers, notably Adler, Jung and Freud. In a peculiar way Dr. Prince, Boston born and educated for the most part in New England, tied together and reaffirmed a tradition of psychologic understanding that had already been expressed by Hawthorne in *The Scarlet Letter* and by Dr. Oliver Wendell Holmes in his novels, as well as in the novels of S. Weir Mitchell, who might be called a New Englander by courtesy.
>
> But Dr. Prince was specific. He hammered home his point, and in many ways his concept is more important than the idea proposed by Robert Louis Stevenson in *Dr. Jekyll and Mr. Hyde* (1886), because "Sally Beauchamp," who was the brainchild of Dr. Morton Prince, had three personalities, which corresponded (approximately) to the present-day concept of ego, super-ego and id.
>
> If there is anyone who has not read *The Dissociation of a Personality*, he would do well to do so and in doing so will learn for himself how thoroughly up-to-date this book is, even though it has passed through five decades of popular reading.

CORRESPONDENCE

"UNJUSTIFIED TERROR?"

To the Editor: In the case of rupture of the uterus published in the Maternal Welfare column in the November 1 issue of the *Journal* we were surprised to find the statement, "This case illustrates several features often seen in maternal death: first and foremost, the often-deprecated but terrifying inherent hazard of repeat cesarean section. . . ."

Thirty-five years ago when the classic technic, with its inherent anatomic deficiencies, was in vogue, this statement might have had some justification since rupture of the uterus after a previous classic cesarean section leads to hemorrhage, shock, extrusion of the fetus into the abdominal cavity and a clinical picture that may indeed be terrifying. It is regrettable that the summary of the case omitted an item that appears to be a very important one: whether the previous section in this case was the old-fashioned classic cesarean section. If so, it should be observed that the classic operation has been vehemently deprecated for many years so that it has been largely supplanted by the far safer low-transverse cervical operation, with the happy result that the principal cause of rupture after cesarean section has been eliminated.

The many advantages of the low-transverse cervical operation have been emphasized so often that they need not be repeated here, but, in a review of 1000 cases of repeat cesarean section we found, as indeed many others have, that the incidence of rupture of the low-transverse cervical scar is less than a fourth of that of rupture of the classic scar. When rupture of the low-transverse cervical scar does occur, it happens at term or during labor, and is associated with minimal shock or hemorrhage; the fetus is usually retained in the uterine cavity, and mother and baby, as a rule, do very well. On the other hand, when rupture follows the classic operation, it is likely to occur before labor and several weeks before term.

That the low cervical operation has eliminated the principal cause of rupture after cesarean section is abundantly clear from the reports of many authors, including Schmitz, Cosgrove and, more recently, Heffernan, Lynch and Dyer, who point out not only that there is little risk in the carefully observed patient in repeat cesarean section but also that the scar is considered sufficiently strong that many of these patients are allowed to go into labor and deliver normally. (In the experience of the Margaret Hague Maternity Center, approximately 50 per cent of the patients have normal deliveries after cesarean section.)

It therefore seems that the only "terrifying inherent hazard of repeat cesarean section" is to be found in the patient who has been subjected to a classic section and who, in subsequent pregnancies, may have signs and symptoms of uterine rupture, which, if not promptly recognized and treated, may lead to disaster.

ROY J. HEFFERNAN, M.D.
WILLIAM A. LYNCH, M.D.
Brookline, Massachusetts

BOOK REVIEWS

Understanding Human Behavior. By James L. McCartney, M.D. 8°, 258 pp., with 12 illustrations. New York: Vantage Press, 1956. $3.50.

There have been books with titles similar to this before, but this one contains a fresh approach. Dr. McCartney has already written two important and interesting books entitled "The Drama of Sex" and "The Frustrated Martyr."

This book is more general and deals with the problem of living in a world where tension and competition stimulate the nervous system more than is absolutely necessary. First of all it is a book written by a doctor out of his own experience. Moreover, the author obviously has a gift for psychologic understanding and a concept of what integration can mean in the personality. He gives due credit to the ever-present issue of frustration; his chapter on guilt is especially good. He deals with dreams in a realistic way and emphasizes the importance of diagnosis as the starting point in treatment. As for sex, "normal" and "abnormal," he defines and describes both kinds. He stresses the field of individual psychotherapy but he does not neglect the benefits inherent in group psychotherapy. As a physician, he emphasizes the use of physical treatment, and he closes his book with a philosophic chapter that could only have been written by an experienced doctor of medicine who has dealt for many years with many people and various problems. The physician will find this book valuable because Dr. McCartney is so precise. The average reader will find it informative and provocative. This book is well organized. It is not sensational, but it is very readable.

MERRILL MOORE, M.D.

Kohlenhydratstoffwechsel, Insulin und Diabetes. By Prof. Dr. Hans Staub. 8°, paper, 48 pp., with 19 illustrations and 6 tables. Stuttgart: Georg Thieme, 1956. DM 9.60.- $2.30. (Distributed in the United States by Intercontinental Medical Book Corporation, New York City.)

This excellent little book is recommended to anyone interested in the metabolism of carbohydrate in insulin and in diabetes. Its author, the head of the medical clinic in Basel and professor in the University, summarized twenty-six years ago the status of carbohydrate metabolism and in the intervening years has taught students and doctors and has been intimately involved with his colleagues in research. The book presents a remarkably clear and concise and almost unbelievably up-to-date review of the literature on current problems in diabetes that doctors want to know about.

The subjects considered include the correlation of the histories of patients with hormones in carbohydrate metabolism, hypophysectomy after cancer of the breast and the Houssay and Long–Lukens phenomena; the so-called free diet in diabetes; fructose in treatment; the ketone bodies; diabetic coma; glucagon; the sulfonamides in diabetic therapy; the chemical constitution of insulin; and a discussion of the mechanism of the action of insulin.

ELLIOTT P. JOSLIN, M.D.

BOOKS RECEIVED

The receipt of the following books is acknowledged, and this listing must be regarded as a sufficient return for the courtesy of the sender. Books that appear to be of particular interest will be reviewed as space permits. Additional information in regard to all listed books will be gladly furnished on request.

Atlas und Praktikum der Dermatologie und Venerologie. By Professor Dr. med. W. Burckhardt, director, Poliklinik for Skin and Venereal Disease in Zurich. 4°, cloth, 279 pp., with 158 illustrations. Munich: Urban and Schwarzenberg, 1955. DM 48.-

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Centennial Papers — Saint Elizabeths Hospital — 1855-1955. Edited by Winfred Overholser, M.D., Sc. D., L.H.D., superintendent, Saint Elizabeths Hospital, Washington, D.C. 8°, cloth, 251 pp., with 8 illustrations and a frontispiece. Washington, D.C.: Centennial Commission, Saint Elizabeths Hospital, 1956.

Tratamiento de las Enfermedades Mentales. By Leo Alexander, M.D., director, Neurological Unit, Division of Psychiatric Research, Boston State Hospital, and instructor in psychiatry, Tufts University School of Medicine. Spanish version by Dr. Antonio Jorge Milano, director, Sanatorio Neuropsiquiatrico "San Gabriel" and Clinica "Esquirol," and chief of service, Neuropsiquiatria del Ministerio de Asistencia Social and Salud Publica. 8°, cloth, 611 pp., with 143 illustrations and 22 tables. Buenos Aires: Editorial Medico Quirurgica, 1956.

Six Children. By Estelle J. Foote, M.D., psychiatrist-in-charge, Traveling School Clinic, Walter E. Fernald State School, Waverley, Massachusetts. 8°, cloth, 317 pp., with charts. Springfield, Illinois: Charles C Thomas, 1956. $5.50.

Autoconditioning: The new way to a successful life. By Hornell Hart, Ph.D., Department of Sociology, Duke University. 8°, cloth, 263 pp., with 3 tables and charts. Englewood Cliffs, New Jersey: Prentice-Hall, Incorporated, 1956. $4.95.

Bericht über die 6. Jahresversammlung der Weltvereinigung für Psychische Hygiene, August 16-22, 1953, Vienna. Edited by Österreichische Gesellschaft für Psychische Hygiene. 8°, paper, 149 pp., with a frontispiece. $3.50. Vienna: Wilhelm Maudrich, 1956. (Distributed in the United States by Intercontinental Medical Book Corporation, New York City.)

Verhandlungen der Deutschen Gesellschaft für Verdauungs- und Stoffwechselkrankheiten: XVIII. Tagung in Bad Homburg 3-5 Oktober, 1955. Edited by Prof. Dr. H. W. Bansi, Hamburg, permanent secretary of the Society. 8°, paper, 300 pp., with 109 illustrations and 32 tables. Stuttgart: Georg Thieme, 1956. DM 48.- $11.40. (Distributed in the United States by Intercontinental Medical Book Corporation, New York City.)

EKG - Fibel. By Dr. Med. Rolf Heinecker, Medizinische Universitätsklinik, Frankfurt am Main. With a foreword by Prof. Dr. Ferdinand Hoff, Frankfurt am Main. 8°, paper, 203 pp., with 216 illustrations. Stuttgart: Georg Thieme, 1956. DM 19.80.- $4.20. (Distributed in the United States by Intercontinental Medical Book Corporation, New York City.)

Expert Committee on Psychiatric Nursing. First report. 8°, paper, 44 pp. Geneva: World Health Organization, 1956. 1/9, Sw. fr. 1.-, $0.30. Available also in French and Spanish editions. (*World Health Organization, Technical Report Series,* No. 105.) (Distributed in the United States by Columbia University Press, New York City.)

Joint FAO/WHO Conference on Food Additives, Geneva, September 19-22, 1955. 8°, paper, 16 pp. Geneva: World Health Organization, 1956. 1/9, Sw. fr. 1.-, $0.30. Available also in French and Spanish editions. (*World Health Organization, Technical Report Series,* No. 107.) (Also, *FAO Nutrition Meetings Report Series,* No. 11.) (Distributed in the United States by Columbia University Press, New York City.)

Expert Committee on Biological Standardization. Ninth report. 8°, paper, 20 pp. Geneva: World Health Organization, 1956. 1/9, Sw. fr. 1.-, $0.30. Also available in French and Spanish editions. (*World Health Organization, Technical Report Series,* No. 108.) (Distributed in the United States by Columbia University Press, New York City.)

Venereal Diseases: A survey of existing legislation. 8°, paper, 44 pp. Geneva: World Health Organization, 1956. 3/6d, Sw. fr. 2.-, $0.70. Available also in French edition. (Offprint from Vol. 7, No. 2, of the *International Digest of Health Legislation.*) (Distributed in the United States by Columbia University Press, New York City.)

Die Lungentuberkulose: Diagnose und Therapie. By Prof. Dr. Med. Paul-Georg Schmidt, head, Westerwaldklinik Waldbreitbach, Tuberkulose-Krankenhaus der LVA Rheinprovinz. Third edition, thoroughly revised. 8°, cloth, 384 pp., with 234 illustrations. Stuttgart: Georg Thieme, 1956. DM 58.- $13.80. (Distributed in the United States by Intercontinental Medical Book Corporation, New York City.)

Clinical Roentgenology: The digestive tract, the gall bladder, liver, and pancreas, the excretory tract and special studies emphasizing differential considerations. Vol. 4. By Alfred A. de Lorimier, M.D., radiologist, Saint Francis Memorial Hospital, San Francisco, consultant in radiology for the United States Army, Letterman Army Hospital, and consultant in radiation therapy, United States Public Health Service at the United States Marine Hospital, San Francisco; Henry G. Moehring, M.D., radiologist, Duluth Clinic, Duluth, Minnesota; and John R. Hannan, M.D., radiologist, Cleveland, and radiologist, Lake County Memorial Hospital, Painesville, Ohio. 4°, cloth, 676 pp., with illustrations. Springfield, Illinois: Charles C Thomas, 1956. $24.50.

Official History of the Canadian Medical Services, 1939-1945: Volume I: Organization and Campaigns. Edited by W. R. Feasby, M.D., lieutenant-colonel, R.C.A.M.C., supplementary reserve lecturer in physiology, University of Toronto. 4°, cloth, 568 pp., with paintings and photographs by Canadian war artists and photographers and maps drawn by Captain C. C. J. Bond and a frontispiece. Ottawa: Edmond Cloutier, C.M.G., A.O., D.S.P., Queen's Printer and Controller of Stationery, 1956. $5.00. (Obtainable from Superintendent of Government Publications, Department of Public Printing and Stationery, Ottawa, Canada.)

Chemosurgery in Cancer, Gangrene and Infections: Featuring a new method for the microscopically controlled excision of cancer. By Frederic E. Mohs, M.D., associate professor of chemosurgery, Department of Surgery, University of Wisconsin Medical School, head of the Chemosurgery Clinic, State of Wisconsin General Hospital, and research associate, McArdle Memorial Laboratory for Cancer Research, Madison, Wisconsin. 8°, cloth, 306 pp., with 225 illustrations and 47 tables. Springfield, Illinois: Charles C Thomas, 1956. $13.50.

Morals in Medicine. By Thomas J. O'Donnell, S.J., regent and professor of medical ethics, Georgetown University School of Medicine and Georgetown University Hospital. 8°, cloth, 281 pp. Westminster, Maryland: The Newman Press, 1956. $3.75.

NOTICES

ANNOUNCEMENT

Dr. Walter J. Pacosa announces the opening of his office at Central Chambers, 16 Center Street, Northampton, Massachusetts, for the practice of pediatrics.

COLLEGE OF GENERAL PRACTICE OF CANADA

The first annual scientific convention of the College of General Practice of Canada will be held at the Sheraton-Mt. Royal Hotel, Montreal, Quebec, March 4-6, 1957. Applications for housing accommodations should be made to Dr. J. Y. Tremblay, 3244 Beaubien, Montreal, Quebec.

Further information may be obtained from Dr. W. V. Johnston, Executive Director, College of General Practice of Canada, 176 St. George Street, Toronto 5, Ontario.

SYMPOSIUM ON FUNDAMENTAL CANCER RESEARCH

The eleventh annual symposium on fundamental cancer research sponsored by the M. D. Anderson Hospital and Tumor Institute will be held at the University of Texas M. D. Anderson Hospital and Tumor Institute, Texas Medical Center, Houston, March 7-9. The general topic for the symposium will be "Viruses and Tumor Growths."

Presentation of the seventh annual Bertner Foundation Award will be made, and the Bertner Lecture will be delivered on Friday evening, March 8.

Further information may be received from the Editorial Office, Room 115, M. D. Anderson Hospital and Tumor Institute, Texas Medical Center, Houston 25, Texas.

SOCIETY MEETINGS AND CONFERENCES

JANUARY 16-19, 1957. International Fertility Association. Page 1109, issue of December 6.
JANUARY 17, 1957. Arthritis Study Unit. Page 831, issue of October 25.
FEBRUARY and APRIL, 1957. Massachusetts Society for Research in Psychiatry. Page 56, issue of July 5.
FEBRUARY 4, 1957. Yale University School of Medicine. Page 1163, issue of December 13.
FEBRUARY 23 and 24, 1957. Los Angeles Radiological Society. Page 1163, issue of December 13.
MARCH 4–6, 1957. College of General Practice of Canada. Page 1205.
MARCH 7–9, 1957. Symposium on Fundamental Cancer Research. Page 1205.
APRIL 27, 1957. Postgraduate Medical Institute. Page 785, issue of October 18.

CALENDAR FOR THE WEEK BEGINNING THURSDAY, DECEMBER 27

THURSDAY, DECEMBER 27
*8:00–8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*8:00–9:00 a.m. Surgical Grand Rounds. Dr. John Spellman and staff. Saint Elizabeth's Hospital.
8:00–9:00 a.m. Medical Journal Club. Joslin Auditorium, New England Deaconess Hospital.
*8:45–9:45 a.m. Cardiac Grand Rounds. Jimmy Fund Building, Children's Medical Center, 35 Binney Street.
*9:00 a.m. Neurological Rounds. Dr. Kane. Evans 2 Conference Room, Massachusetts Memorial Hospitals.
*9:00–10:00 a.m. Surgical Rounds. Sherman Auditorium, Beth Israel Hospital.
*9:00–10:00 a.m. Arthritis Grand Rounds. Robert Breck Brigham Hospital.
*9:00–10:00 a.m. Grand Rounds. Russell Room, House of the Good Samaritan.
*10:00–11:00 a.m. Combined Medical-Surgical Rounds. Sherman Auditorium, Beth Israel Hospital.
*10:15 a.m. Clinicopathological Staff Conference. Massachusetts Memorial Hospitals.
*10:15 a.m.–12:00 m. Medical Grand Rounds. Dr. Keefer. Evans 8 Amphitheater, Massachusetts Memorial Hospitals.
10:30–11:15 a.m. Lecture on Diabetes for Doctors and Patients by Members and Guests of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*11:00 a.m.–12:00 m. Medical Grand Rounds. Dr. Sylvester McGinn and staff. Saint Elizabeth's Hospital.
*11:00 a.m.–12:00 m. Medical Staff Conference. Sherman Auditorium, Beth Israel Hospital.
*11:00 a.m.–12:00 m. Pediatric Conference. Mount Auburn Hospital, Cambridge.
*11:00 a.m.–12:30 p.m. Hand Clinic (Physical Medicine and Rehabilitation Service). Boston City Hospital.
*12:00 m. Clinicopathological Conference. Dr. Benjamin Castleman and associates. Pathology Amphitheater, Massachusetts General Hospital.
*12:15–1:15 p.m. Orthopedic Clinic. Amphitheater, Peter Bent Brigham Hospital.
*3:30 p.m. Gastroenterology Conference. Dr. Ingelfinger. Massachusetts Memorial Hospitals.

FRIDAY, DECEMBER 28
*8:00–8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*8:00–9:00 a.m. Members and Guests of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*9:30–11:30 a.m. Medical and Surgical Grand Rounds. Drs. George W. Thorn and Francis D. Moore. Main Amphitheater, Peter Bent Brigham Hospital.
*10:00 a.m. Tuberculosis Surgical Clinic. South End Health Unit, 57 East Concord Street.
*10:00 a.m. Ward Rounds. Massachusetts Memorial Hospitals.
10:30–11:15 a.m. Lecture on Diabetes for Doctors and Patients by Members and Guests of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*11:00 a.m.–12:30 p.m. Medical Grand Rounds. Stearns Auditorium, New England Center Hospital.
*11:30 a.m. Tumor Clinic. Drs. Soutter and Lemon. Robinson 4, Massachusetts Memorial Hospitals.
*12:00 m. Urological Conference. Dr. C. J. E. Kickham, presiding. Auditorium, Carney Hospital, Dorchester.
*12:00 m. Pediatric Grand Rounds. Thorndike Amphitheater, Boston City Hospital.
*12:30–1:30 p.m. Surgical Grand Rounds. Stearns Auditorium, New England Center Hospital.
*1:30 p.m. Fertility and Endocrine Clinic. Free Hospital for Women, Brookline.
*1:30 p.m. Tumor Clinic. Mount Auburn Hospital, Cambridge.
*2:00–3:00 p.m. Pathology Conference. Dr. James Graham. Saint Elizabeth's Hospital.
*4:00–6:00 p.m. X-Ray Conference. Dr. Merrill C. Sosman. Stearns Auditorium, New England Center Hospital.
*4:00–10:00 p.m. Alcoholism Clinic. By appointment. Washingtonian Hospital, 41 Morton Street, Jamaica Plain.
*4:30 p.m. Neuroradiologic Conference. X-Ray Conference Room, New England Deaconess Hospital.

SATURDAY, DECEMBER 29
*8:00–8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*8:30–10:00 a.m. Orthopedic Staff Conference. Boston City Hospital.
*9:00–10:00 a.m. Anesthesiology Conference. Dr. Benjamin Etsten. Anesthesia Laboratory, New England Center Hospital.
*9:30–11:00 a.m. Surgical House Officers' Conference. Second-Floor Conference Room, Carney Hospital, Dorchester.
*9:30 a.m.–12:00 m. Grand Rounds. Haynes Memorial Hospital, Brookline.
*10:00 a.m. Ward Rounds. Massachusetts Memorial Hospitals.
*10:30 a.m. Teaching Ward Rounds. Ward South 2, Free Hospital for Women.
10:30–11:15 a.m. Lecture on Diabetes for Doctors and Patients by Members and Guests of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*11:00 a.m.–12:00 m. Hematology Conference. Dr. William Dameshek. Stearns Auditorium, New England Center Hospital.

MONDAY, DECEMBER 31
*8:00–8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*10:00 a.m. Ward Rounds. Massachusetts Memorial Hospitals.
10:30–11:15 a.m. Lecture on Diabetes for Doctors and Patients by Members and Guests of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*11:00 a.m.–12:30 p.m. Staff Conference. Child Psychiatry. By appointment. Conference Room (Burnham 7), Massachusetts General Hospital.
*12:00 m.–1:00 p.m. Pediatric Clinicopathological Conference. Pratt Lecture Hall, Joseph H. Pratt Diagnostic Hospital.
*12:00 m.–1:00 p.m. Staff Meeting. Obstetrical and Gynecological. Drs. Abrams and Parker. Evans 8 Amphitheater, Massachusetts Memorial Hospitals.
*12:00 m.–1:00 p.m. Tumor Conference. Dr. C. C. Lund and members of the Tumor Board. Dowling Amphitheater, Boston City Hospital.
*12:15–1:15 p.m. Clinicopathological Conference. Main Amphitheater, Peter Bent Brigham Hospital.
*1:00 p.m. Alcoholism Clinic. Peter Bent Brigham Hospital.
*2:00–3:00 p.m. X-Ray Conference. Dr. William Carey. Saint Elizabeth's Hospital.
*3:00–4:00 p.m. Neuroradiologic Conference. Dr. Bertram Selverstone. Stearns Auditorium, New England Center Hospital.
*4:00–5:30 p.m. Anesthesiology Conference. Dr. Benjamin Etsten. Stearns Auditorium, New England Center Hospital.
*5:00–6:30 p.m. Anesthesiology Group of the Lahey Clinic. Joslin Auditorium, New England Deaconess Hospital.
5:15 p.m. Staff Meeting. Harris Hall, New England Deaconess Hospital.
*7:00–9:00 p.m. Slide Seminar in Pathology. Dr. Edward T. MacMahon. Stearns Auditorium, New England Center Hospital.

TUESDAY, JANUARY 1
Holiday

WEDNESDAY, JANUARY 2
*8:00–8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*8:00–9:00 a.m. Medical and Surgical Clinic on Diabetic Problems. Deaconess II, New England Deaconess Hospital.
*8:00–9:00 a.m. Surgical Grand Rounds. Auditorium, Carney Hospital, Dorchester.
*9:00–10:00 a.m. Surgical Grand Rounds. Dr. Smithwick. Evans 8 Amphitheater, Massachusetts Memorial Hospitals.
*10:00 a.m. Ward Rounds. Massachusetts Memorial Hospitals.
10:30–11:15 a.m. Lecture on Diabetes for Doctors and Patients by Members and Guests of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
11:00 a.m. Orthopedic Grand Rounds. Bigelow Amphitheater, White 3A, Massachusetts General Hospital.
*11:00 a.m.–12:00 m. Pediatric Conference for Practitioners. Jimmy Fund Building, Children's Medical Center, 35 Binney Street.
*12:00 m.–1:00 p.m. Boston State Hospital Psychiatry Seminar. Reception Building Auditorium, 591 Morton Street, Dorchester.
*12:00 m.–1:00 p.m. Roentgen Diagnostic Conference. 5th-floor teaching unit, Beth Israel Hospital.
*12:00 m.–1:00 p.m. Neurology, Neurosurgery and Psychiatry Conference. Drs. John F. Sullivan, Justin Hope and Bertram Selverstone. Stearns Auditorium, New England Center Hospital.
*12:00 m.–1:00 p.m. Pediatric Medical-Surgical Rounds. Pratt Lecture Hall, Joseph H. Pratt Diagnostic Hospital.
*12:00 m. Pediatric Clinicopathological Conference. Jimmy Fund Building, Children's Medical Center, 35 Binney Street.
*12:15 p.m. Vascular Rounds. Drs. Edward A. Edwards and Chilton Crane. D-Main, Peter Bent Brigham Hospital.
*12:30–1:30 p.m. Weekly Staff Review of Autopsies. Dr. William A. Meissner. Joslin Auditorium, New England Deaconess Hospital.
*1:00 p.m. Alcoholism Clinic. Peter Bent Brigham Hospital.
*1:00 p.m. Massachusetts General Hospital Hand Clinic. The Clinics of the Massachusetts General Hospital.
*1:00–2:00 p.m. Surgical Staff Meeting. Dr. Smithwick. Evans Conference Room, Massachusetts Memorial Hospitals.
*2:00 p.m. Rectal Clinic. Peter Bent Brigham Hospital.
*2:00 p.m. Vascular Rounds. Robinson 4, Massachusetts Memorial Hospitals.
*2:00–3:00 p.m. Pediatric Conference for Practitioners. Jimmy Fund Building, Children's Medical Center, 35 Binney Street.
*4:00–5:30 p.m. Fracture Lecture. Boston City Hospital.
*4:00–6:00 p.m. Overholt Thoracic Conference. Joslin Auditorium, New England Deaconess Hospital.
*6:00 p.m. Alcoholism Clinic. Peter Bent Brigham Hospital.
*6:30 p.m. Lahey Clinic Lectures. Radiography of the Esophagus — "Why and How." Dr. Esther Silveus. Joslin Auditorium, New England Deaconess Hospital.

*Open to the medical profession.